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(21) International Application Number: PCT/US95/09339 (22) International Filing Date: 24 July 1995 (24.07.95) (30) Priority Data: 08/279,472 22 July 1994 (22.07.94) US (71) Applicants: DEMETER BIOTECHNOLOGIES, LTD. [US/US]; Suite 19-D, 905 W. Main Street, Brightleaf Square, Durham, NC 27701 (US). UNITED STATES OF AMERICA, as represented by THE SECRETARY OF AGRICULTURE [US/US]; Washington, DC 20250-1400 (US). (72) Inventors: GARBARINO, Joan; 1709 Curtis Street, Berkeley, CA 94702 (US). JAYNES, Jesse; 2417 Highridge Road, Raleigh, NC 27606 (US). BELKNAP, William; 1012 Key Route Boulevard, Albany, CA 94706 (US). (74) Agents: NORRIS, Lawrence, G. et al.; Rothwell, Figg, Ernst & Kurz, Suite 701, East Tower, 555 Thirteenth Street, N.W., Washington, DC 20004 (US).			(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: UBIQUITIN-LYTIC PEPTIDE FUSION GENE CONSTRUCTS, PROTEIN PRODUCTS DERIVING THEREFROM, AND METHODS OF MAKING AND USING SAME			
(57) Abstract Stabilized ubiquitin-lytic peptide fusion polypeptides and a method of making the same by sub-cloning nucleic acid sequences coding for lytic peptides into a plasmid vector comprising a promoter and ubiquitin polypeptide coding sequence, wherein the ubiquitin polypeptide sequence is linked to the 5' end of the lytic peptide nucleic acid sequence and is translated as a fusion polypeptide.			

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**UBIQUITIN-LYTIC PEPTIDE FUSION GENE CONSTRUCTS, PROTEIN PRODUCTS
DERIVING THEREFROM, AND METHODS OF MAKING AND USING SAME**

5

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Application No. 08/231,730, filed April 20, 1994 in the names of Jesse M. Jaynes and Gordon R. Julian, which in turn is a continuation of
10 Application No. 08/225,476, filed April 8, 1994 in the names of Jesse M. Jaynes and Gordon R. Julian, which is in turn a continuation of Application No. 08/148,491, filed November 8, 1993 and Application No. 08/148,889, filed November 8, 1993, both filed in the name of Gordon R. Julian, which are in turn continuations
15 of Application No. 08/039,620, filed June 4, 1993 in the name of Jesse M. Jaynes and Gordon R. Julian.

BACKGROUND OF THE INVENTION

20 Field of the Invention

The present invention relates to ubiquitin-lytic peptide fusion gene constructs with enhanced stability and gene expression, ubiquitin-lytic peptide fusion protein products, and methods of making and using the same.

25

Description of Related Art

Naturally occurring lytic peptides play an important if not critical role as immunological agents in insects and have some, albeit secondary, defense functions in a range of other animals.
30 The function of these peptides is to destroy prokaryotic and other non-host cells by disrupting the cell membrane and promoting cell lysis. Common features of these naturally occurring lytic peptides include an overall basic charge, a small size (23-39 amino acid residues), and the ability to form amphipathic α -
35 helices or β -pleated sheets. Several types of lytic peptides have been identified: cecropins (described in U.S. Patents 4,355,104

and 4,520,016 to Hultmark et al.), defensins, sarcotoxins, melittin, and magainins (described in U.S. Patent No. 4,810,777 to Zasloff). Each of these peptide types is distinguished by sequence and secondary structure characteristics.

5 Several hypotheses have been suggested for the mechanism of action of the lytic peptides: disruption of the membrane lipid bilayer by the amphipathic α -helix portion of the lytic peptide; lytic peptide formation of ion channels, which results in osmotically induced cytolysis; lytic peptide promotion of protein
10 aggregation, which results in ion channel formation; and lytic peptide-induced release of phospholipids. Whatever the mechanism of lytic peptide-induced membrane damage, an ordered secondary conformation such as an amphipathic α -helix and positive charge density are features that appear to participate in the function of
15 the lytic peptides.

Active synthetic analogs of naturally occurring lytic peptides have been produced and tested in vitro against a variety of prokaryotic and eukaryotic cell types (see for example Arrowood, M.J., et al., J. Protozool. 38: 161s [1991]; Jaynes, J.M., et al., FASEB J. 2: 2878 [1988]), including: gram positive
20 and gram negative bacteria, fungi, yeast, protozoa, envelope viruses, virus-infected eukaryotic cells, and neoplastic or transformed mammalian cells. The results from these studies indicate that many of the synthetic lytic peptide analogs have
25 similar or higher levels of lytic activity for many different types of cells, compared to the naturally occurring forms. In addition, the peptide concentration required to lyse microbial pathogens such as protozoans, yeast, and bacteria does not lyse normal mammalian cells. However, because previous work
30 demonstrates that absolute sequence is not important as long as positive charge and amphipathy are preserved, the level of activity for a given synthetic peptide is difficult to predict.

The specificity of the lytic action also depends upon the concentration of the peptide and the type of membrane with which
35 it interacts. Jaynes, J.M. et al., Peptide Research 2: 157 (1989) discuss the altered cytoskeletal characteristics of transformed or

neoplastic mammalian cells that make them susceptible to lysis by the peptides. In these experiments, normal, human non-transformed cells remained unaffected at a given peptide concentration while transformed cells were lysed; however, when normal cells were
5 treated with the cytoskeletal inhibitors cytochalasin D or colchicine, sensitivity to lysis increased. The experiments show that the action of lytic peptides on normal mammalian cells is limited. This resistance to lysis was most probably due to the well-developed cytoskeletal network of normal cells. In contrast,
10 transformed cell lines which have well-known cytoskeletal deficiencies were sensitive to lysis. Because of differences in cellular sensitivity to lysis, lytic peptide concentration can be manipulated to effect lysis of one cell type but not another at the same locus.

15 Synthetic lytic peptide analogs can also act as agents of eukaryotic cell proliferation. Peptides that promote lysis of transformed cells will, at lower concentrations, promote cell proliferation in some cell types. This stimulatory activity is thought to depend on the channel-forming capability of the
20 peptides, which somehow stimulates nutrient uptake, calcium influx or metabolite release, thereby stimulating cell proliferation (see Jaynes, J.M., Drug News & Perspectives 3: 69 [1990]; and Reed, W.A. et al., Molecular Reproduction and Development 31: 106 [1992]). Thus, at a given concentration, these peptides stimulate
25 or create channels that can be beneficial to the normal mammalian cell in a benign environment where it is not important to exclude toxic compounds.

The synthetic lytic peptide analogs typically contain as few as 12 and as many as 40 amino acid residues. A phenylalanine
30 residue is often positioned at the amino terminus of the protein to provide an aromatic moiety analogous to the tryptophan residue located near the amino terminus of natural cecropins and a UV-absorbing moiety with which to monitor the purification of the synthetic peptide. The basis for the design of these lytic
35 peptide analogs is that a peptide of minimal length, having an

amphipathic α -helical structural or a β -pleated sheet motif, and overall positive charge density effects lytic activity.

Plant disease is one of the leading causes of crop loss in the world and is estimated to cause up to one third of total crop loss worldwide; for example, in the potato losses associated with bacterial disease are as high as 25% of worldwide production. Additionally, the cultivation of a few species of plants in a concentrated area exacerbates the spread of disease. Recent advances in genetic engineering have lead to the development of plants with disease resistant phenotypes based on the expression of recombinant DNA molecules. Transgenic tobacco plants were engineered with both a wound inducible PiII promoter and a constitutive 35S promoter to express two lytic peptides (SHIVA-1 and SB-37) with bacteriolytic activity. The SHIVA-1 plant demonstrated enhanced resistance to bacterial wilt caused by infection by *Pseudomonas solanacearum* (Jaynes, J.M., et al., Plant Science 89: 43 (1993); Destefano-Beltran, L., et al., Biotechnology in Plant Disease Control, pp. 175-189, Wiley-Liss (1993). Thus lytic peptides have valuable uses as anti-phytopathogenic agents. However, chemical synthesis of these lytic peptides is very expensive. Therefore, alternate, more economical and efficient methods of synthesis are needed, such as in vivo synthesis in host cells using recombinant DNA methods.

Recombinant DNA molecules are produced by sub-cloning genes into plasmids using a bacterial host intermediate. In principle this technique is straightforward. However, any sequence that interferes with bacterial growth through replication or production of products toxic to the bacteria, such a lytic peptides, are difficult to clone. Often, host bacterial cells containing mutated forms of the DNA sequences encoding toxic products will be selected. These mutations can result in either decreased expression or production of an inactive product. Bacteria will even insert mutations that prevent expression of a potentially toxic product in cloned genes controlled by a eukaryotic promoter that is not active in prokaryotes. The effect of this selection of mutated species leads to an inability to isolate sub-clones

containing a non-mutated gene of choice. Thus, some sub-cloned genes are unstable in their bacterial hosts, although this instability can only be shown empirically. The bacteriolytic activity of the lytic peptides is an obstacle to the production of stable recombinant DNA molecules that express the genes at high levels.

For example, in an attempt to sub-clone into a standard plasmid vector a gene coding for frog magainin, a natural lytic peptide, bacterial transformants contained deletion mutations in the magainin coding region. Another attempt was made to sub-clone a synthetic lytic peptide (SEQ ID NO. 98) into a standard plasmid vector (pUC19) containing the Cauliflower Mosaic Virus 35S promoter. The resulting transformants were screened by polymerase chain reaction (PCR). However, out of 30 colonies, only 2 sub-clones gave faint positive signals. These two sub-clones were sequenced. The sequence showed that one clone had a point mutation that introduced a stop codon 3/4 of the way through the lytic peptide, and the other clone had a point mutation that changed the start codon from methionine to isoleucine. Both mutations would prevent the biosynthesis of the protein. Four more clones were analyzed, and of these four, one was sub-cloned in the wrong orientation, and three others had mutations introduced into the sequence. One of these sub-clones was selected for further analysis, but it inhibited the growth of its *E. coli* host. Thus, the production of recombinant DNA molecules coding for lytic peptides is difficult due to the uncertainty in obtaining the correct sub-clone.

Ubiquitin is a small, highly conserved protein present in all eukaryotes. Ubiquitins are encoded by gene families that are characterized by two types of basic structures. Polyubiquitin genes contain several direct repeats of ubiquitin, and ubiquitin-ribosomal fusion genes encode a single ubiquitin unit fused to the coding region for a small ribosomal associated protein. Both of these gene types are translated as polyproteins and then are processed by an endogenous ubiquitin hydrolase present in eukaryotes to release multiple ubiquitin proteins or ubiquitin and

the ribosomal associated protein. A number of ubiquitin cDNAs or genomic clones have been isolated, including plant ubiquitin cDNAs and genomic clones from the potato (Garbarino, J. and Belknap, W., Plant Molecular Biology 24: 119 (1994); Garbarino, J. et al., Plant Molecular Biology 20: 235 (1992)).

U.S. Patents 5,093,242 and 5,132,213 to Bachmair et al. teach the use of a ubiquitin cloning vector as a method of producing specified protein amino-termini. A recombinant DNA molecule was constructed with a protein coding gene fused at its amino terminus to a ubiquitin coding gene. Due to translation as a polypeptide and cleavage by hydrolases, a protein with any amino acid at the amino terminus can be generated. The amino terminus can be used to control the metabolic stability of the protein. However, the metabolic stability of the protein is dependent on the resulting amino acid at the amino-terminus, not the generation of a translation polypeptide.

The forgoing facts suggest that although lytic peptides as a class may include species that are efficacious in destroying bacteria, neoplastic cells, fungi, virus-infected cells, and protozoa, this lytic characteristic also decreases the stability of sub-cloned lytic peptides in host cells. This decreased stability hinders efforts to develop a more economical and efficient means of synthesizing lytic peptides.

It would therefore be a significant advance in the art, and is correspondingly an object of the present invention to develop a method of sub-cloning nucleotide sequences coding for lytic peptides into expression vectors, providing gene constructs with enhanced stability and gene expression and reduced toxicity.

30

SUMMARY OF THE INVENTION

The present invention relates generally to ubiquitin-lytic peptide fusion nucleic acid expression vectors comprising a promoter and ubiquitin polypeptide coding sequence ligated to a lytic peptide, ubiquitin-lytic peptide fusion protein products,

and methods of making and using the same, as hereinafter more fully described.

It is another object of the invention to provide ubiquitin-lytic peptide fusion expression vectors and protein products
5 derived therefrom.

It is another object of the invention to provide ubiquitin-lytic peptide fusion expression vectors that are expressed in plants having utility for promoting wound healing and combatting bacterial infections in plants.

10 It is a further object of this invention to provide ubiquitin-lytic peptide fusion polypeptides having utility for combatting protozoal infections, neoplasias, fungal infections, viral infections, and bacterial infections in mammals and plants.

It is yet another object of this invention to develop a
15 method of sub-cloning polypeptide sequences in ubiquitin-fusion expression vectors with enhanced stability and gene expression.

It is yet another object of this invention to provide expression vectors containing constitutive and wound inducible ubiquitin promoters that are expressed in eukaryotic cells.

20 It is yet another object of this invention to provide expression vectors with prokaryotic promoters that express ubiquitin-lytic peptide fusion genes in prokaryotic hosts, the products of which can be cleaved in vitro by ubiquitin hydrolases.

These and other objects and advantages will be more fully
25 apparent from the ensuing disclosure and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a map of a recombinant nucleic acid expression
30 vector pUCUbi3-LP98 containing a 920 bp ubiquitin-ribosomal fusion gene promoter region linked to a 228 bp coding region for a ubiquitin polypeptide with a six bp BamHI site at the 3' end (SEQ ID NO. 93) that is fused at its 3' end to a gene coding for a lytic peptide (D5D*, SEQ ID NO. 98). The Ubi3 ubiquitin-lytic
35 peptide nucleotide sequence corresponds to SEQ ID NO. 92. A

nopaline synthase polyadenylation signal is located at the 3' end of the lytic peptide gene.

Figure 2 is a map of a recombinant nucleic acid expression vector pUCUbi7-LP98 containing a 1220 bp polyubiquitin promoter region and 568 bp intron linked to a 228 bp coding region for a ubiquitin polypeptide with a six bp BamHI site at the 3' end (SEQ ID NO. 96) that is fused at its 3' end to a gene coding for a lytic peptide (D5D*, SEQ ID NO. 98). The Ubi7 ubiquitin-lytic peptide nucleotide sequence corresponds to SEQ ID NO. 95. A nopaline synthase polyadenylation signal is located at the 3' end of the lytic peptide gene.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS THEREOF

15

The disclosures of prior co-pending U.S. Patent Application No. 08/039,620 filed June 4, 1993 in the names of Jesse M. Jaynes and Gordon R. Julian, U.S. Patent Application No. 08/148,889 filed November 8, 1993 in the name of Gordon R. Julian, U.S. Patent Application No. 08/148,491 filed November 8, 1993 in the name of Gordon R. Julian, U.S. Patent Application No. 08/225,476 filed April 8, 1994 in the names of Jesse M. Jaynes and Gordon R. Julian, and U.S. Patent Application No. 08/231,730 filed April 20, 1994 in the names of Jesse M. Jaynes and Gordon R. Julian, are all hereby incorporated herein by reference in their entirety.

The term "amphipathic" as used herein refers to the distribution of hydrophobic and hydrophilic amino acid residues along opposing faces of an α -helix structure or other secondary conformation, which results in one face of the α -helix structure being predominantly hydrophobic and the other face being predominantly hydrophilic. The degree of amphipathy of a peptide can be assessed by plotting the sequential amino acid residues on an Edmanson helical wheel (see also Kamtekar, S. et al., Science 262: 1680 (1993)).

The terms "peptide" and "polypeptide" as used herein refer to a molecule composed of a chain of amino acid residues and is

intended to be construed as inclusive of polypeptides and peptides per se having molecular weights of up to 10,000 daltons, as well as proteins having molecular weights of greater than about 10,000 daltons, wherein the molecular weights are number average molecular weights. The term is also intended to be construed as inclusive of functional equivalents thereof when used in reference to a specific peptide coding sequence in the specification and claims herein. Functional equivalents of peptides and polypeptides include but are not limited to deletions, additions, and substitutions of amino acids in the polypeptide or peptide chain that do not adversely affect the overall function of the resulting peptide or polypeptide.

The term "plasmid" as used herein refers to a DNA molecule that is capable of autonomous replication within a host cell, either extrachromosomally or as part of the host cell chromosome(s). The starting plasmids herein are commercially available, are publicly available on an unrestricted basis, or can be constructed from such available plasmids as disclosed herein and/or in accordance with published procedures. In certain instances, as will be apparent to the ordinarily skilled artisan, other plasmids known in the art may be used interchangeable with plasmids described herein.

The term "ligation" as used herein refers to the process of forming phosphodiester bonds between two double-stranded DNA fragments. Unless otherwise specified, ligation is accomplished using standard procedures known to one skilled in the art.

The term "polymerase chain reaction," or "PCR" as used herein refers to a method for amplification of a desired nucleotide sequence in vitro, as described in U.S. Patent No. 4,683,195, herein incorporated by reference in its entirety.

The term "nucleic acid" as used herein refers to deoxyribonucleic acid molecules (DNA) composed of a chain of deoxyribonucleotides and ribonucleic acid molecules (RNA) composed of a chain of ribonucleotides. The term "nucleic acid" as used herein is to be construed as including functional equivalents thereof when used in reference to a specific nucleotide sequence

in the specification and claims herein. Functional equivalents of nucleic acid molecules include synonymous coding sequences with one or more codon substitutions and deletions or additions that do not effect the overall function of the resulting nucleic acid molecule. The degeneracy of the genetic code is well known to the art; therefore, synonymous coding sequences with one or more codon substitutions can be readily determined by one of ordinary skill in the art. Synonymous nucleotide coding sequences vary from the exemplified coding sequences but encode proteins of the same amino acid sequences as those specifically provided herein or proteins with similar function and are therefore also regarded as functional equivalents thereof.

The term "promoter" as used herein refers to an untranslated (i.e. one that does not result in a peptide or protein product) sequence upstream of the polypeptide coding region of a nucleotide sequence that controls transcription of a gene. Promoters typically fall into two classes, constitutive and inducible. Inducible promoters initiate high levels of transcription of the nucleic acid under their control in response to external stimuli. Constitutive promoters maintain a relatively constant level of transcription in a given cell. Suitable promoters for use in the present may include both prokaryotic and eukaryotic promoters, with all ubiquitin promoters being preferred, solanaceous plant ubiquitin promoters being highly preferred, and potato ubiquitin promoters being most preferred. Additional control sequences such as ribosomal binding sites and enhancers may be included as control sequences when necessary.

The term "polyadenylation site" as used herein refers to a control sequence located on the 3' end of a gene construct that provides a signal for cleavage and polyadenylation of the transcription unit expressed from the promoter. These control sequences are known to one skilled in the art

The term "expression" as used herein refers to transcription and /or translation of a nucleic acid sequence coding for a protein or peptide.

In one embodiment, the present invention is directed to an isolated nucleotide sequence comprising a gene coding for a ubiquitin polypeptide and functional equivalents thereof, linked to a ubiquitin promoter and functional equivalents thereof.

5 Suitable ubiquitin promoters for use in the present invention include, but are not limited to, ubiquitin promoters from solanaceous plants. Preferably, the ubiquitin promoter is a potato plant ubiquitin promoter and most preferably it is the potato Ubi3 or Ubi7 promoter. In embodiments wherein the isolated
10 nucleotide sequence codes for the potato Ubi3 promoter linked to a gene coding for a ubiquitin polypeptide it has a nucleotide sequence according to SEQ ID NO. 93. The Ubi3 promoter alone also has utility as constitutive promoter in eukaryotes.

In embodiments wherein the isolated nucleotide sequence codes
15 for the potato Ubi7 promoter linked to a gene coding for a ubiquitin polypeptide it has a nucleotide sequence according to SEQ ID NO. 96. The Ubi7 nucleotide sequence according to SEQ ID NO. 96 includes an intron that is part of the ubiquitin transcription unit. The intron is not required for gene
20 expression from the Ubi7 promoter, thus the Ubi7 promoter region without the intron can be considered as a specific functional equivalent of the Ubi7 promoter. The Ubi7 promoter alone, with or without the intron, has utility as a wound inducible promoter in eukaryotes.

25 Preferably, the nucleotide sequence comprising the isolated ubiquitin promoter and gene coding for a ubiquitin polypeptide further comprises a gene coding for a lytic peptide ligated to the 3' end of the gene coding for a ubiquitin polypeptide. Suitable genes coding for a lytic peptide have a nucleotide sequence coding
30 for any one of the amino acid sequences according to SEQ ID NO. 1-91 and 97-98.

In one preferred embodiment, the present invention is directed to an isolated nucleotide sequence comprising a gene coding for a lytic peptide ligated to the 3' end of the gene
35 coding for a ubiquitin polypeptide linked to the Ubi3 ubiquitin promoter having a nucleotide sequence according to SEQ ID NO. 92.

In an alternative of this embodiment, the present invention is directed to an isolated nucleotide sequence comprising a gene coding for a lytic peptide ligated to the 3' end of the gene coding for a ubiquitin polypeptide linked to a Ubi7 ubiquitin promoter having a nucleotide sequence according to SEQ ID NO. 95.

In another embodiment, the present invention is directed to a recombinant nucleic acid expression vector. The vector is characterized in that it comprises a nucleotide sequence wherein a gene coding for a ubiquitin polypeptide is linked to a ubiquitin promoter. Preferably, the present invention is directed to a recombinant nucleic acid expression vector characterized in that it further comprises a nucleotide sequence wherein a gene coding for a lytic peptide is ligated to the 3' end of the gene coding for a ubiquitin polypeptide linked to a ubiquitin promoter. Suitable vectors for use in this invention include any eukaryotic or prokaryotic expression vectors known in the art. Preferable vectors for use in this invention are pUC19 and pCGN1547.

In another embodiment, the present invention is directed to a host cell that is transformed by a recombinant DNA expression vector comprising a gene coding for a ubiquitin polypeptide linked to a ubiquitin promoter. Suitable host cells for transformation in the present invention include all known bacterial host cells, with all strains of *Escherichia coli* and *Agrobacterium tumefaciens* being preferred. Preferably, the present invention is directed to a host cell the recombinant DNA expression vector further comprises a gene coding for a lytic peptide ligated to the 3' end of the gene coding for a ubiquitin polypeptide linked to a ubiquitin promoter. Suitable genes coding for a lytic peptide have a nucleotide sequence coding for any one of the amino acid sequences according to SEQ ID NO. 1-91 and 97-98.

Preferably, the present invention is directed to a solanaceous plant host cell that is transformed by a recombinant DNA expression vector. Most preferably the solanaceous plant cell is a potato plant host cell.

In another embodiment, the present invention is directed to an isolated nucleotide sequence and functional equivalents thereof

coding for a lytic peptide, where the nucleotide sequence has a sequence coding for any one of the amino acid sequences according to SEQ ID NO. 1-91 and 97-98.

5 In yet another embodiment, the present invention is directed to a purified ubiquitin polypeptide and functional equivalents thereof having an amino acid sequence according to SEQ ID NO. 94. This embodiment can further comprise a lytic peptide translationally fused to the carboxy terminus of a ubiquitin polypeptide.

10 In another embodiment, the present invention is directed to a method of sub-cloning nucleotide sequences coding for lytic peptides and expressing such sequences in cells. The method comprises a first step wherein a recombinant nucleic acid containing a gene coding for a lytic peptide ligated to a gene
15 coding for a ubiquitin polypeptide linked to a ubiquitin promoter is produced in a first host cell. Suitable first host cells include any known bacterial host cells. Preferably, the first host cell is either an *Escherichia coli* cell or an *Agrobacterium tumefaciens* cell.

20 If the peptides are sub-cloned using such a ubiquitin-fusion expression vector, the following advantage results: the lytic peptide gene constructs have increased stability in the bacterial host. While not wishing to be bound by any one theory, the present inventors believe that the stability is due to the
25 ubiquitin protein coding nucleic acid region fused to the 5' end of the lytic peptide nucleic acid sequence. Bacteria do not contain the endogenous hydrolase necessary for cleavage of the ubiquitin fusion protein, so the gene constructs are not toxic to bacteria, since active lytic peptide cannot be released. Thus
30 functional equivalents of the ubiquitin fusion polypeptide include any ubiquitin molecule that is capable of deceiving the host cell into viewing the gene construct and its products as non-toxic.

In a variation of this embodiment, the recombinant nucleic acid vector is isolated from the first host cell and expressed in
35 a second host cell. Suitable second host cells are plant and animal cells, preferably a solanaceous plant cell, and most

preferably a potato plant cell. In the second host cell the fusion gene is expressed at high levels and the polyprotein is cleaved by endogenous ubiquitin hydrolases to produce active lytic peptide. These transgenic hosts provide from the expression
5 vector lytic peptides in vivo to combat bacterial infections, fungal infections, protozoal infections, virus infections, and neoplasias. In addition, expression vectors containing ubiquitin promoters that are either constitutive or wound inducible are used to express peptides in eukaryotes.

10 The present invention is also directed to a method of sub-cloning nucleotide sequences coding for lytic peptides and expressing such sequences in cells. The method comprises producing in a host cell a recombinant nucleic acid expression vector comprising a gene coding for a lytic peptide ligated to the 3' end
15 of a gene coding for a ubiquitin promoter linked to a prokaryotic promoter sequence. Suitable prokaryotic promoters include those known to one skilled in the art to be active in prokaryotes and used in plasmid vectors for bacterial gene expression.

The recombinant nucleic acid expression vector is expressed
20 in the host cell and ubiquitin-lytic peptide fusion polypeptides are isolated from the host. Preferably, the host cell is either an *Escherichia coli* cell or an *Agrobacterium tumefaciens* cell. The isolated ubiquitin-lytic peptide fusion polypeptides are then cleaved in vitro by ubiquitin hydrolases to release the lytic
25 peptides from the ubiquitin polypeptide (see U.S. Patent No. 5,196,321 to Bachmair et al.). The active lytic peptides are then used to treat bacterial infections, fungal infections, protozoal infections, virus infections, and neoplasias. These isolated lytic peptides are in some instances glyoxylated or methylated in
30 vitro to stabilize against proteolytic digestion in vivo.

Ubiquitin fusion expression vectors thus have broad utility as cloning and expression vectors to stabilize and sub-clone lytic peptides nucleotide sequences, as well as a wide variety of protein coding nucleic acid sequences that are otherwise toxic to
35 their hosts. The ubiquitin-lytic peptide expression vectors also have broad utility as an economical and efficient means to

synthesize lytic peptides in host cells. These lytic peptides have utility for combatting protozoal infections, neoplasias, fungal infections, viral infections, and bacterial infections in mammals and plants.

- 5 The features and advantages of the invention are more fully shown by the following illustrative examples and embodiments, which are not to be limitingly construed as regard the broad scope, utility, and applicability of the invention.

10

Example 1

Representative Lytic Peptides and Ubiquitin polypeptide

- Set out in Table 1 below as illustrative examples of lytic peptides are the amino acid sequences of families of related lytic peptides. These lytic peptides are designated for ease of reference as SEQ ID NO. 1-91 and 97-98. Nucleic acid sequences coding for these lytic peptides and functional equivalents thereof represent examples of lytic peptide nucleic acid sequences that are sub-cloned to make ubiquitin-lytic peptide fusion gene constructs and polypeptides. The ubiquitin polypeptide, designated for ease of reference as SEQ ID NO. 94, and functional equivalents thereof, represents an example of the 5' fusion ubiquitin polypeptide.

25

TABLE 1: LYTIC PEPTIDE SEQUENCES

SEQ ID NO. 1

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys

1 5 10 15

30

Lys Ala Val Lys Lys Ala Val Lys Lys Lys Lys

20 25

SEQ ID NO. 2

Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Lys Lys Ala

35 1 5 10 15

Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala Val Lys Lys Lys Lys
 20 25 30

SEO ID NO. 3

5 Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Ala Val Lys
 1 5 10 15
 Ala Val Lys Lys Ala Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala
 20 25 30
 Val Lys Lys Lys Lys
 10 35

SEO ID NO. 4

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
 1 5 10 15
 15 Lys Ala Val Lys Lys Ala Val
 20

SEO ID NO. 5

Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Lys Lys Ala
 20 1 5 10 15
 Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala Val
 20 25

SEO ID NO. 6

25 Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Ala Val Lys
 1 5 10 15
 Ala Val Lys Lys Ala Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala
 20 25 30
 Val
 30

SEO ID NO. 7

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
 1 5 10 15
 Arg Gly Val Arg Lys Val Ala Lys Arg Lys Arg
 35 20 25

SEO ID NO. 8

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
 1 5 10 15
 Arg Gly Val Arg Lys Val Ala
 5 20

SEO ID NO. 9

Lys Arg Lys Arg Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu
 1 5 10 15
 10 Ala Arg Lys Ile Ala Arg Leu Gly Val Ala Phe
 20 25

SEO ID NO. 10

Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu Ala Arg Lys Ile
 15 1 5 10 15
 Ala Arg Leu Gly Val Ala Phe
 20

SEO ID NO. 11

20 Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
 1 5 10 15
 Arg Gly Val Arg Lys Val Ala Lys Arg Lys Arg Lys Lys Asp Leu
 20 25 30

25 SEO ID NO. 12

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
 1 . 5 10 15
 Arg Gly Val Arg Lys Val Ala Lys Asp Leu
 20 25

30

SEO ID NO. 13

Lys Arg Lys Arg Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu
 1 5 10 15
 Ala Arg Lys Ile Ala Arg Leu Gly Val Ala Phe Lys Asp Leu
 35 20 25 30

SEQ ID NO. 14

Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu Ala Arg Lys Ile
 1 5 10 15
 Ala Arg Leu Gly Val Ala Phe Lys Asp Leu
 5 20 25

SEQ ID NO. 15

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15
 10 Ala Lys Lys Val Ala Lys Val Ala Val Ala Val
 20 25

SEQ ID NO. 16

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 15 1 5 10 15
 Ala Lys Lys Val Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Val
 20 25 30

SEQ ID NO. 17

20 Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15
 Ala Lys Lys Val Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Lys
 20 25 30
 Val Ala Val Ala Val
 25 35

SEQ ID NO. 18

Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val Ala Lys Lys Val
 1 5 10 15
 30 Ala Lys Val Ala Val Ala Val
 20

SEQ ID NO. 19

Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val Ala Lys Lys Val
 35 1 5 10 15
 Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Val
 20 25

SEQ ID NO. 20

Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val Ala Lys Lys Val
 1 5 10 15
 5 Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Lys Val Ala Val Ala
 20 25 30
 Val

SEQ ID NO. 21

10 Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val
 1 5 10 15
 Ala Lys Val Ala Lys Lys Val Ala Lys Lys Val
 20 25

15 SEQ ID NO. 22

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val
 1 5 10 15
 Ala Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala
 20 25 30

20

SEQ ID NO. 23

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val
 1 5 10 15
 Ala Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala
 25 20 25 30
 Lys Val Ala Lys Lys
 35 .

SEQ ID NO. 24

30 Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15
 Lys Lys Val Ala Lys Lys Val
 20

SEO ID NO. 25

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15
 Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala
 5 20 25

SEO ID NO. 26

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15
 10 Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Val Ala Lys
 20 25 30
 Lys

SEO ID NO. 27

15 Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15
 Lys Lys Val Ala Lys Lys Val Lys Lys Lys Lys
 20 25

20 SEO ID NO. 28

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15
 Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Lys Lys Lys
 20 25 30

25

SEO ID NO. 29

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15
 Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Val Ala Lys
 30 20 25 30
 Lys Lys Lys Lys Lys
 35

SEO ID NO. 30

35 Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Lys Lys Lys Lys
 1 5 10 15

SEQ ID NO. 31

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 1 5 10 15
 5 Ala Lys Lys Lys Lys
 20

SEQ ID NO. 32

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 10 1 5 10 15
 Ala Lys Val Lys Ala Lys Val Lys Lys Lys Lys
 20 25

SEQ ID NO. 33

15 Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 1 5 10

SEQ ID NO. 34

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 20 1 5 10 15
 Ala

SEQ ID NO. 35

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 25 1 5 10 15
 Ala Lys Val Lys Ala Lys Val
 20

SEQ ID NO. 36

30 Lys Lys Lys Lys Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 1 5 10 15

SEQ ID NO. 37

Lys Lys Lys Lys Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
 35 1 5 10 15

Ala Lys Val Lys Ala
20

SEO ID NO. 38

5 Lys Lys Lys Lys Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15
Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val
20 25

10 SEO ID NO. 39

Phe Lys Lys Val Lys Lys Val Ala Lys Lys Val Cys Lys Cys Val Lys
1 5 10 15
Lys Ala Val Lys Lys Val Lys Lys Phe
20 25

15

SEO ID NO. 40

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
1 5 10 15
Lys Ala Val Lys Lys Ala Val Cys Cys Cys Cys
20 20 25

SEO ID NO. 41

Cys Cys Cys Cys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
1 5 10 15
25 Ala Lys Lys Val Ala Lys Val Ala Val Ala Val
20 25

SEO ID NO. 42

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
30 1 5 10 15
Lys Ala Val Lys Lys Ala Val Ser Ser Ser Ser
20 25

SEO ID NO. 43

35 Ser Ser Ser Ser Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
1 5 10 15

Ala Lys Lys Val Ala Lys Val Ala Val Ala Val
 20 25

SEO ID NO. 44

5 Phe Ala Leu Ala Leu Lys Ala Leu Lys Lys Ala Leu Lys Lys Leu Lys
 1 5 10 15
 Lys Ala Leu Lys Lys Ala Leu
 20

10 SEO ID NO. 45

Leu Ala Lys Lys Leu Ala Lys Lys Leu Lys Lys Leu Ala Lys Lys Leu
 1 5 10 15
 Ala Lys Leu Ala Leu Ala Phe
 20

15

SEO ID NO. 46

Phe Ala Phe Ala Phe Lys Ala Phe Lys Lys Ala Phe Lys Lys Phe Lys
 1 5 10 15
 Lys Ala Phe Lys Lys Ala Phe
 20 20

SEO ID NO. 47

Phe Ala Ile Ala Ile Lys Ala Ile Lys Lys Ala Ile Lys Lys Ile Lys
 1 5 10 15
 25 Lys Ala Ile Lys Lys Ala Ile
 20

SEO ID NO. 48

Phe Ala Lys Lys Phe Ala Lys Lys Phe Lys Lys Phe Ala Lys Lys Phe
 30 1 5 10 15
 Ala Lys Phe Ala Phe Ala Phe
 20

SEO ID NO. 49

Phe Lys Arg Leu Ala Lys Ile Lys Val Leu Arg Leu Ala Lys Ile Lys
 1 5 10 15
 Arg

5

SEO ID NO. 50

Lys Leu Lys Leu Ala Val Lys Leu Val Gly Leu Leu Arg Lys Lys Arg
 1 5 10 15
 Ala Leu Lys Ile Ala Leu Arg Gly Val Ala Lys Arg Ala Gly Arg Leu
 10 20 25 30
 Ala Val Arg Lys Phe
 35

SEO ID NO. 51

15 Phe Ala Arg Ala Arg Lys Ala Arg Lys Lys Ala Arg Lys Lys Arg Lys
 1 5 10 15
 Lys Ala Arg Lys Lys Ala Arg Lys Asp Arg
 20 25

SEO ID NO. 52

20 Phe Ala Val Ala Val Cys Ala Val Cys Cys Ala Val Cys Cys Val Cys
 1 5 10 15
 Cys Ala Val Cys Cys Ala Val
 20

25

SEO ID NO. 53

Phe Ala Val Ala Val Ser Ala Val Ser Ser Ala Val Ser Ser Val Ser
 1 5 10 15
 Ser Ala Val Ser Ser Ala Val
 30 20

SEO ID NO. 54

Phe Ala Val Ala Val Ser Ala Val Ser Ser Ala Val Ser Ser Val Ser
 1 5 10 15
 35 Ser Ala Val Ser Ser Ala Val Ser Ser Ser Ser
 20 25

SEO ID NO. 55

Phe Ala Lys Lys Phe Ala Lys Lys Phe Lys Lys Phe Ala Lys Lys Phe
 1 5 10 15
 5 Ala Lys Phe Ala Phe Ala Phe Lys Lys Lys Lys
 20 25

SEO ID NO. 56

Lys Lys Lys Lys Phe Ala Lys Lys Phe Ala Lys Lys Phe Lys Lys Phe
 10 1 5 10 15
 Ala Lys Lys Phe Ala Lys Phe Ala Phe Ala Phe
 20 25

SEO ID NO. 57

15 Phe Ala Arg Lys Phe Leu Lys Arg Phe Lys Lys Phe Val Arg Lys Phe
 1 5 10 15
 Ile Arg Phe Ala Phe Leu Phe
 20

20 SEO ID NO. 58

Phe Ala Arg Lys Phe Leu Lys Arg Phe Lys Lys Phe Val Arg Lys Phe
 1 5 10 15
 Ile Arg Phe Ala Phe Leu Phe Lys Arg Lys Arg
 20 25

25

SEO ID NO. 59

Lys Arg Lys Arg Phe Ala Arg Lys Phe Leu Lys Arg Phe Lys Lys Phe
 1 5 10 15
 Val Arg Lys Phe Ile Arg Phe Ala Phe Leu Phe
 30 20 25

SEO ID NO. 60

Ile Ala Lys Lys Ile Ala Lys Lys Ile Lys Lys Ile Ala Lys Lys Ile
 1 5 10 15
 35 Ala Lys Ile Ala Ile Ala Ile
 20

SEO ID NO. 61

Ile Ala Lys Lys Ile Ala Lys Lys Ile Lys Lys Ile Ala Lys Lys Ile
 1 5 10 15
 5 Ala Lys Ile Ala Ile Ala Ile Lys Lys Lys Lys
 20 25

SEO ID NO. 62

Lys Lys Lys Lys Ile Ala Lys Lys Ile Ala Lys Lys Ile Lys Lys Ile
 10 1 5 10 15
 Ala Lys Lys Ile Ala Lys Ile Ala Ile Ala Ile
 20 25

SEO ID NO. 63

15 Ile Ala Arg Lys Ile Leu Lys Arg Ile Lys Lys Ile Val Arg Lys Phe
 1 5 10 15
 Ile Arg Ile Ala Ile Leu Ile
 20

20 SEO ID NO. 64

Ile Ala Arg Lys Ile Leu Lys Arg Ile Lys Lys Ile Val Arg Lys Phe
 1 5 10 15
 Ile Arg Ile Ala Ile Leu Ile Lys Arg Lys Arg
 20 25

25

SEO ID NO. 65

Lys Arg Lys Arg Ile Ala Arg Lys Ile Leu Lys Arg Ile Lys Lys Ile
 1 5 10 15
 Val Arg Lys Phe Ile Arg Ile Ala Ile Leu Ile
 30 20 25

SEO ID NO. 66

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 35 Leu

SEO ID NO. 67

Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
 1 5 10 15
 Ala Lys Ile Lys Leu
 5 20

SEO ID NO. 68

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 10 Leu Lys Arg Lys Arg
 20

SEO ID NO. 69

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 15 1 5 10 15
 Leu Arg Val Lys Leu Lys Ile
 20

SEO ID NO. 70

20 Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 Leu Arg Val Lys Leu Lys Ile Lys Arg Lys Arg
 20 25

SEO ID NO. 71

25 Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
 1 5 10 15
 Ala Lys Ile Lys Leu Arg Val Lys Leu Lys Ile
 20 25

30

SEO ID NO. 72

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 Leu Arg Val Lys Leu Lys Ile Arg Ala Arg Ile Lys Leu
 35 20 25

SEQ ID NO. 73

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 Leu Arg Val Lys Leu Lys Ile Arg Ala Arg Ile Lys Leu Lys Arg Lys
 5 20 25 30
 Arg

SEQ ID NO. 74

Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
 10 1 5 10 15
 Ala Lys Ile Lys Leu Arg Val Lys Leu Lys Ile Arg Ala Arg Ile Lys
 20 25 30
 Leu

SEQ ID NO. 75

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 Leu Val Phe Ala Ile Leu Leu
 20

20

SEQ ID NO. 76

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15
 Leu Val Phe Ala Ile Leu Leu Lys Arg Lys Arg
 25 20 25

SEQ ID NO. 77

Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
 1 5 10 15
 30 Ala Lys Ile Lys Leu Val Phe Ala Ile Leu Leu
 20 25

SEQ ID NO. 78

Val Phe Ala Ile Leu Leu Phe Lys Leu Arg Ala Lys Ile Lys Val Arg
 35 1 5 10 15

Leu Arg Ala Lys Ile Lys Leu
20

SEO ID NO. 79

5 Val Phe Ala Ile Leu Leu Phe Lys Leu Arg Ala Lys Ile Lys Val Arg
1 5 10 15
Leu Arg Ala Lys Ile Lys Leu Lys Arg Lys Arg
20 25

10 SEO ID NO. 80

Lys Arg Lys Arg Val Phe Ala Ile Leu Leu Phe Lys Leu Arg Ala Lys
1 5 10 15
Ile Lys Val Arg Leu Arg Ala Lys Ile Lys Leu
20 25

15

SEO ID NO. 81

Val Gly Glu Cys Val Arg Gly Arg Cys Pro Ser Gly Met Cys Cys Ser
1 5 10 15
Gln Phe Gly Tyr Cys Gly Lys Gly Pro Lys Tyr Cys Gly
20 25

SEO ID NO. 82

Val Gly Glu Cys Val Arg Gly Arg Cys Pro Ser Gly Met Cys Cys Ser
1 5 10 15
25 Gln Phe Gly Tyr Cys Gly Lys Gly Pro Lys Tyr Cys Gly Arg
20 25 30

SEO ID NO. 83

Leu Gly Asp Cys Leu Lys Gly Lys Cys Pro Ser Gly Met Cys Cys Ser
30 1 5 10 15
Asn Tyr Gly Phe Cys Gly Arg Gly Pro Arg Phe Cys Gly Lys
20 25 30

SEO ID NO. 84

35 Gln Cys Ile Gly Asn Gly Gly Arg Cys Asn Glu Asn Val Gly Pro Pro
1 5 10 15

Tyr Cys Cys Ser Gly Phe Cys Leu Arg Gln Pro Gly Gln Gly Tyr Gly
 20 25 30
 Tyr Cys Lys Asn Arg
 35

5

SEQ ID NO. 85

Cys Ile Gly Asn Gly Gly Arg Cys Asn Glu Asn Val Gly Pro Pro Tyr
 1 5 10 15
 Cys Cys Ser Gly Phe Cys Leu Arg Gln Pro Asn Gln Gly Tyr Gly Val
 10 20 25 30
 Cys Arg Asn Arg
 35

SEQ ID NO. 86

15 Cys Ile Gly Gln Gly Gly Lys Cys Gln Asp Gln Leu Gly Pro Pro Phe
 1 5 10 15
 Cys Cys Ser Gly Tyr Cys Val Lys Asn Pro Gln Asn Gly Phe Gly Leu
 20 25 30
 Cys Lys Gln Lys
 20 35

SEQ ID NO. 87

Gln Lys Leu Cys Glu Arg Pro Ser Gly Thr Trp Ser Gly Val Cys Gly
 1 5 10 15
 25 Asn Asn Asn Ala Cys Lys Asn Gln Cys Ile Asn Leu Glu Lys Ala Arg
 20 25 30
 His Gly Ser Cys Asn Tyr Val Phe Pro Ala His Lys
 35 40

30 SEQ ID NO. 88

Gln Arg Val Cys Asp Lys Pro Ser Gly Thr Trp Ser Gly Leu Cys Gly
 1 5 10 15
 Asn Asn Asn Ala Cys Arg Gln Asn Cys Ile Gln Val Asp Arg Ala Lys
 20 25 30
 35 Lys Gly Ser Cys Gln Phe Leu Tyr Pro Ala Lys Lys
 35 40

SEO ID NO. 89

Gln Lys Leu Cys Gln Arg Pro Ser Gly Thr Trp Ser Gly Val Cys Gly
 1 5 10 15
 5 Asn Asn Asn Ala Cys Lys Asn Gln Cys Ile Arg Leu Glu Lys Ala Arg
 20 25 30
 His Gly Ser Cys
 35

10 SEO ID NO. 90

Gln Arg Val Cys Asn Lys Pro Ser Gly Thr Trp Ser Gly Leu Cys Gly
 1 5 10 15
 Asn Asn Asn Ala Cys Arg Gln Asn Cys Ile Lys Val Asp Arg Ala Lys
 20 25 30
 15 Lys Gly Ser Cys
 35

SEO ID NO. 91

Met Leu Glu Glu Leu Phe Glu Glu Met Thr Glu Phe Ile Glu Glu Val
 20 1 5 10 15
 Ile Glu Thr Met
 20

SEO ID NO. 94

25 Met Gln Ile Phe Val Lys Thr Leu
 1 5
 Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr
 10 15 20
 Ile Asp Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
 30 25 30 35
 Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu
 40 45 50
 Glu Asp Gly Arg Thr Leu Ala Asp Tyr Asn Ile Gln Lys Glu
 55 60
 35 Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Gly Ser
 65 70 75

SEQ ID NO. 97

Lys Arg Lys Arg Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu
 1 5 10 15
 5 Ala Arg Lys Ile Ala Arg Leu Gly Val Ala Lys Leu Ala Gly Leu Arg
 20 25 30
 Ala Val Leu Lys Phe
 35

10 SEQ ID NO. 98

Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu Asp Arg Lys Ile
 1 5 10 15
 Asp Arg Leu Gly Val Asp Phe
 20

15

Example 2

Construction of Ubiquitin-lytic Peptide Fusion Plasmids With
Ubiquitin-ribosomal Fusion Gene Promoter (Ubi3)

20 Exemplary and preferred pUC19 and pCGN1547 plasmid vectors containing a potato (*Solanum tuberosum*) ubiquitin-ribosomal fusion promoter (Ubi3), a region coding for a ubiquitin polypeptide, and a gene coding for a lytic peptide are constructed.

25 To obtain the genomic clone containing a ubiquitin-ribosomal fusion promoter and ubiquitin polypeptide coding region, a λ FIXII potato genomic library is first prescreened using PCR. The PCR primers are homologous to regions of the ubiquitin-ribosomal fusion cDNA (see Garbarino J., et al., Plant Molecular Biology 20: 235(1992); Garbarino J. and Bellmap W., Plant Molecular Biology
 30 24: 119 (1994); both of which are hereby incorporated by reference herein in their entirety). A primer 5' to the beginning ATG of ubiquitin and a primer complementary to a sequence near the 5' end of the ribosomal protein are used.

The library is plated in 22 aliquots containing approximately
 35 0.5×10^6 pfu (plaque forming units) each on an *E. coli* lawn. A plug is taken from each of the 22 resulting plaques and the eluant from

each is subjected to PCR under standard conditions. The PCR products are run on agarose gels. The gels are then blotted and probed with the ubiquitin coding region of the ubiquitin-ribosomal fusion cDNA according to standard conditions. Two of the plugs produce PCR products that hybridize to the cDNA probe. Both of these are the correct size for the predicted ubiquitin-ribosomal fusion genomic fragment.

The eluants from these two plugs are then plated and screened with the ubiquitin coding region of the ubiquitin-ribosomal fusion cDNA according to standard conditions. For verification, the positive plaques from the initial screen are replated and screened with a probe containing both the ribosomal protein-coding region and the 3' end of the potato ubiquitin-ribosomal fusion cDNA.

The genomic clones are sequenced using Sequenase version 2.0 (United States Biochemical Corporation) or Promega fmol DNA Sequencing System using standard conditions. A genomic clone containing both the ubiquitin-ribosomal fusion promoter region and the ubiquitin-ribosomal fusion coding region is identified.

A chimeric gene is then constructed with a portion of the potato ubiquitin-ribosomal fusion genomic clone ligated to a lytic peptide gene. PCR is used to generate the Ubi3 promoter and ubiquitin portion of the chimeric gene. The Ubi3 promoter region includes the 920 bp promoter region upstream of the ubiquitin ATG, and the ubiquitin polypeptide coding region is 228 bp plus 6 bp of a BamHI restriction site at the 3' end (SEQ ID NO. 93). The primers contain BamHI restriction sites and are homologous to the 5' end of the Ubi3 promoter and to the 3' end of the ubiquitin polypeptide coding region. The ubiquitin-ribosomal fusion genomic clone is used as the amplification template. This insert is first sub-cloned into the plasmid pCGN1547, as described in Garbarino et al., Plant Molecular Biology 24: 119 (1994). The Ubi3 insert is then isolated from pCGN1547 using the BamHI sites and ligated into pUC19 under standard conditions. Transformation of *E. coli* is done according to standard conditions and correct sub-clones are confirmed by mini-prep or PCR DNA analysis. This plasmid is designated pUCUbi3.

A nucleotide fragment coding for the lytic peptide (corresponding to the amino acid sequence SEQ ID NO. 98) is synthesized using a nucleic acid synthesizer, adding a stop codon to the 3' end, and used as a PCR template. The 5' PCR primer homologous to the lytic peptide nucleotide sequence contains a BamHI site, and the 3' primer contains an XbaI site. These sites are used to sub-clone the PCR generated insert into pUC19. A nopaline synthase polyadenylation signal (NOS3') is then cloned 3' to the lytic peptide sequence. Following sequence analysis, the BamHI insert containing the Ubi3 promoter and ubiquitin coding region (SEQ ID NO. 93) is cloned 5' to the lytic peptide.

After transforming *E. coli* under standard conditions, pUC19 sub-clones are selected for mini-prep or PCR DNA analysis according to standard conditions. The direction of the promoter is confirmed and the junction sequences are verified by sequencing according to standard conditions. The resulting Ubi3-ubiquitin-lytic peptide fusion gene construct corresponds to SEQ ID NO. 92. Unlike previous cloning attempts using the CaMV35S promoter, as described in the Background section, the sequence does not reveal any point mutations in the lytic peptide sub-clones. The plasmid is stable in the *E. coli* host and did not inhibit its growth.

The resulting pUC19 recombinant plasmid is shown in the plasmid map in Figure 1. The sequence for the Ubi3-ubiquitin insert containing the ubiquitin-ribosomal fusion gene promoter and the ubiquitin coding region corresponds to SEQ ID NO. 93 in Table 2 below. The sequence for the chimeric Ubi3 ubiquitin-lytic peptide fusion gene construct corresponds to SEQ ID NO. 92 in Table 2 below. This plasmid is designated as pUCUbi3-LP98.

The entire Ubi3 ubiquitin-lytic peptide fusion gene construct, including the polyadenylation site, was isolated from pUC19 as an Asp718/HindIII restriction fragment and sub-cloned into the pCGN1547 *Agrobacterium* vector for use in plant transformation (see McBride, et al., *Plant Molecular Biology* 14: 269 (1990)). This plasmid is designated as pCGNUbi3-LP98.

35

TABLE 2: NUCLEOTIDE SEQUENCE OF POTATO UBIQUITIN-RIBOSOMAL FUSION PROMOTER (UBI3) AND UBIQUITIN CODING REGION INSERT, AND UBIQUITIN-LYTIC PEPTIDE FUSION GENE CONSTRUCT

5	<u>SEQ ID NO. 92</u>	
	CCAAAGCACA TACTTATCGA TTAAATTTTC ATCGAAGAGA TTAATATCGA	50
	ATAATCATAT ACATACTTTA AATACATAAC AAATTTTAAA TACATATATC	100
10	TGGTATATAA TTAATTTTTT AAAGTCATGA AGTATGTATC AAATACACAT	150
	ATGGAAAAAA TTAACATATC ATAATTTAAA AAATAGAAAA GATACATCTA	200
	GTGAAATTAG GTGCATGTAT CAAATACATT AGGAAAAGGG CATATATCTT	250
15	GATCTAGATA ATTAACGATT TTGATTTATG TATAATTTCC AAATGAAGGT	300
	TTATATCTAC TTCAGAAATA ACAATATACT TTTATCAGAA CATTCAACAA	350
20	AGCAACAACC AACTAGAGTG AAAAATACAC ATTGTTCTCT AGACATACAA	400
	AATTGAGAAA AGAATCTCAA AATTTAGAGA AACAAATCTG AATTTCTAGA	450
	AGAAAAAAT AATTATGCAC TTGCTATTG CTCGAAAAAT AAATGAAAGA	500
25	AATTAGACTT TTTTAAAAGA TGTTAGACTA GATATACTCA AAAGCTATTA	550
	AAGGAGTAAT ATTCTTCTTA CATTAAGTAT TTTAGTTACA GTCCTGTAAT	600
30	TAAAGACACA TTTTAGATTG TATCTAAACT TAAATGTATC TAGAATACAT	650
	ATATTTGAAT GCATCATATA CATGTATCCG ACACACCAAT TCTCATAAAA	700
	AACGTAATAT CCTAAACTAA TTTATCCTTC AAGTCAACTT AAGCCCAATA	750
35	TACATTTTCA TCTCTAAAGG CCCAAGTGGC ACAAATGTC AGGCCCAATT	800
	ACGAAGAAAA GGGCTTGTA AACCCTAATA AAGTGGCACT GGCAGAGCTT	850
40	ACACTCTCAT TCCATCAACA AAGAAACCCT AAAAGCCGCA GCGCCACTGA	900
	TTTCTCTCCT CCAGGCGAAG ATG CAG ATC TTC GTG AAG ACC TTA	944
	Met Gln Ile Phe Val Lys Thr Leu	
	1 5	
45	ACG GGG AAG ACG ATC ACC CTA GAG GTT GAG TCT TCC GAC ACC	986
	Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr	
	10 15 20	
50	ATC GAC AAT GTC AAA GCC AAG ATC CAG GAC AAG GAA GGG ATT	1028
	Ile Asp Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile	
	25 30 35	

5 CCC CCA GAC CAG CAG CGT TTG ATT TTC GCC GGA AAG CAG CTT 1070
 Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu 50
 40 45
 5 GAG GAT GGT CGT ACT CTT GCC GAC TAC AAC ATC CAG AAG GAG 1112
 Glu Asp Gly Arg Thr Leu Ala Asp Tyr Asn Ile Gln Lys Glu 60
 55
 10 TCA ACT CTC CAT CTC GTG CTC CGT CTC CGT GGT GGT 1148
 Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly 75
 65 70
 15 GGA TCC GCT GTT AAA AGA GTG GGT CGT AGG TTG AAA AAG TTG 1190
 Gly Ser Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu 90
 80 85
 20 GAC CGT AAG ATT GAT AGG TTA GGA GTT GAT TTT TGATC 1228
 Asp Arg Lys Ile Asp Arg Leu Gly Val Asp Phe 100
 95 100

SEQ ID NO. 93

CCAAAGCACA TACTTATCGA TTTAAATTTTC ATCGAAGAGA TTAATATCGA 50
 25 ATAATCATAT ACATACTTTA AATACATAAC AAATTTTAAA TACATATATC 100
 TGGTATATAA TTAATTTTTT AAAGTCATGA AGTATGTATC AAATACACAT 150
 ATGGAAAAAA TTAACATATC ATAATTTAAA AAATAGAAAA GATACATCTA 200
 30 GTGAAATTAG GTGCATGTAT CAAATACATT AGGAAAAGGG CATATATCTT 250
 GATCTAGATA ATTAACGATT TTGATTTATG TATAATTTCC AAATGAAGGT 300
 35 TTATATCTAC TTCAGAAATA ACAATATACT TTTATCAGAA CATTCAACAA 350
 AGCAACAACC AACTAGAGTG AAAAATACAC ATTGTTCTCT AGACATACAA 400
 AATTGAGAAA AGAATCTCAA AATTTAGAGA AACAAATCTG AATTTCTAGA 450
 40 AGAAAAAAT AATTATGCAC TTTGCTATTG CTCGAAAAAT AAATGAAAGA 500
 AATTAGACTT TTTTAAAAGA TGTTAGACTA GATATACTCA AAAGCTATTA 550
 45 AAGGAGTAAT ATTCTTCTTA CATTAAGTAT TTTAGTTACA GTCCTGTAAT 600
 TAAAGACACA TTTTAGATTG TATCTAAACT TAAATGTATC TAGAATACAT 650
 ATATTTGAAT GCATCATATA CATGTATCCG ACACACCAAT TCTCATAAAA 700
 50 AACGTAATAT CCTAAACTAA TTTATCCTTC AAGTCAACTT AAGCCCAATA 750
 TACATTTTCA TCTCTAAAGG CCAAGTGGC ACAAATGTC AGGCCCAATT 800

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ACGAAGAAAA GGGCTTGTA AACCCTAATA AAGTGGCACT GGCAGAGCTT 850
ACACTCTCAT TCCATCAACA AAGAAACCCCT AAAAGCCGCA GCGCCACTGA 900
5 TTTCTCTCCT CCAGGCGAAG ATG CAG ATC TTC GTG AAG ACC TTA 944
   Met Gln Ile Phe Val Lys Thr Leu
   1 5
10 ACG GGG AAG ACG ATC ACC CTA GAG GTT GAG TCT TCC GAC ACC 986
   Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr
   10 15 20
15 ATC GAC AAT GTC AAA GCC AAG ATC CAG GAC AAG GAA GGG ATT 1028
   Ile Asp Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
   25 30 35
20 CCC CCA GAC CAG CAG CGT TTG ATT TTC GCC GGA AAG CAG CTT 1070
   Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu
   40 45 50
25 GAG GAT GGT CGT ACT CTT GCC GAC TAC AAC ATC CAG AAG GAG 1112
   Glu Asp Gly Arg Thr Leu Ala Asp Tyr Asn Ile Gln Lys Glu
   55 60
30 TCA ACT CTC CAT CTC GTG CTC CGT CTC CGT GGT GGT GGA TCC 1154
   Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Gly Ser
   65 70 75

```

Example 3

Construction of Ubiquitin-lytic Peptide Fusion Plasmids With Polyubiquitin Promoter and Intron (Ubi7)

Exemplary and preferred pUC19 and pCGN1547 plasmid vectors containing a potato (*Solanum tuberosum*) polyubiquitin promoter and intron (Ubi7)', a region coding for a ubiquitin polypeptide, and a gene coding for a lytic peptide are constructed.

To obtain the genomic clone containing a polyubiquitin promoter, intron and ubiquitin polypeptide coding region, a λ FIXII potato genomic library was first prescreened using PCR as described in Example 2 above. The PCR primers are homologous to regions of the polyubiquitin cDNA (see Garbarino J., et al., Plant Molecular Biology 20: 235(1992)). A primer homologous to the 5' untranslated region of ubiquitin in the polyubiquitin cDNA and a primer complementary to the amino terminus of the ubiquitin coding

region in the polyubiquitin cDNA are used. A genomic clone containing both the polyubiquitin promoter region, intron, and the polyubiquitin coding region was identified.

5 A chimeric gene is then constructed with a portion of the potato polyubiquitin genomic clone ligated to a lytic peptide gene, as described in Example 2. PCR is used to generate the Ubi7-ubiquitin portion of the chimeric gene. The Ubi7 promoter region includes the 1220 bp promoter and 568 bp intron upstream of the ubiquitin ATG, and the ubiquitin polypeptide coding region is
10 228 bp plus 6 bp of a BamHI restriction site (SEQ ID NO. 96). This plasmid is designated pUCUbi7.

A nucleotide fragment coding for the lytic peptide (corresponding to the amino acid sequence SEQ ID NO. 98) is generated as described in Example 2. The resulting Ubi7
15 ubiquitin-lytic peptide fusion gene construct corresponds to SEQ ID NO. 95. Unlike previous cloning attempts using the CaMV35S promoter as described in the Background section, the sequence does not reveal any point mutations in the lytic peptide sub-clones. The plasmid was stable in the *E. coli* host and did not inhibit its
20 growth.

The resulting pUC19 recombinant plasmid is shown in the plasmid map in Figure 2. The sequence for the PCR insert containing the polyubiquitin promoter, intron, and the ubiquitin coding region corresponds to SEQ ID NO. 96 in Table 3 below. The
25 sequence for the chimeric Ubi7 ubiquitin-lytic peptide fusion gene construct corresponds to SEQ ID NO. 95 in Table 3 below. This plasmid is designated as pUCUbi7-LP98.

The entire Ubi7 ubiquitin-lytic peptide fusion gene construct, including the polyadenylation site, is isolated from
30 pUC19 as an Asp718/partial HindIII restriction fragment (the intron has an internal HindIII site) and sub-cloned into the pCGN1547 *Agrobacterium* vector for use in plant transformation. This plasmid is designated pCGNUbi7-LP98.

**TABLE 3: NUCLEOTIDE SEQUENCE OF POTATO POLYUBIQUITIN PROMOTER
REGION (UBI7) AND UBIQUITIN CODING REGION INSERT, AND UBIQUITIN-
LYTIC PEPTIDE FUSION GENE CONSTRUCT**

5	<u>SEQ ID NO. 95</u>	
	TTTATCAATC AGATTGGAAC ATATAAATAA ATATAAATTG TCTCAATAAT	50
	TCTACATTAA ACTAATATTT GAAATCTCAA TTTTATGATT TTTTAAATTC	100
10	ACTTTATATC CAAGACAATT TNCANCTTCA AAAAGTTTTA TTAAANATTT	150
	ACATTAGTTT TGTGATGAG GATGACAAGA TNTTGGTCAT CAATTACATA	200
	TACCCAAATT GAATAGTAAG CAACTTCAAT GTTTTTCATA ATGATAATGA	250
15	CAGACACAAN NNAACCCAT TTATTATTCA CATTGATTGA GTTTTATATG	300
	CAATATAGTA ATAATAATAA TATTCTTAT AAAGCAAGAG GTCAATTTTT	350
20	TTTTAATTAT ACCACGTCAC TAAATTATAT TTGATAATGT AAAACAATTC	400
	AAATTTTACT TAAATATCAT GAAATAAACT ATTTTATAA CCAAATTACT	450
	AAATTTTTC C AATAAAAAA AGTCATTAAG AAGACATAAA ATAAATTGA	500
25	GGTAAANGAG TGAAGTCGAC TGACTTTTTT TTTTTTTATC ATAAGAAAAT	550
	AAATTATTAA CTTTAACCTA ATAAAACACT AATATAATTT CATGGAATCT	600
30	AATACTTACC TCTTAGAAAT AAGAAAAAGT GTTCTAATA GACCCCTCAAT	650
	TTACATTAAA TATTTTCAAT CAAATTTAAA TAACAAATAT CAATATGAGG	700
	TCAATAACAA TATCAAAATA ATATGAAAAA AGAGCAATAC ATAATATAAG	750
35	GGACGATTTA AGTGCGATTA TCAAGGTAGT ATTATATCCT AATTGCTAA	800
	TATTTGNGCT CETATATTTA AGGTCATGTT CATGATAAAC TTGAAATGCG	850
40	CTATATTAGA GCATATATTA AAATAAAAAA ATACCTAAAA TAAAATTAG	900
	TTATTTTTAG TATATATTTT TTTACATGAC CTACATTTTT CTGGGTTTTT	950
	CTAAAGGAGC GTGTAAGTGT CGACCTCATT CTCCTAATTT TCCCCACCAC	1000
45	ATAAAAAATTA AAAAGGAAAG GTAGCTTTTG CGTGTGTTTT TGGTACACTA	1050
	CACCTCATTA TTACACGTGT CCTCATATAA TTGGTTAACC CTATGAGGCG	1100
50	GTTCGTCTA GAGTCGGCCA TGCCATCTAT AAAATGAAGC TTTCTGCACC	1150
	TCATTTTTTT CATCTTCTAT CTGATTTCTA TTATAATTTT TCTCAATTGC	1200

	CTTCAAATTT CTCTTTAAGG TTAGAATCTT CTCTATTTTT	1240
	GGTTTTTGTA TGTTTAGATT CTCGAATTAG CTAATCAGGC GCTGTTATAG	1290
5	CCCTTCCTTT TGAGTCTCTC CTCGGTTGTC TTGATGGAAA AGGCCTAACA	1340
	TTTGAGTTTT TTTACGTCTG GTTTGATGGA AAAGGCCTAC AATTGGCCGT	1390
10	TTTCCCGTT CGTTTTGATG AAAAAGCCCC TAGTTTGAGA TTTTTTTTCT	1440
	GTCGTTCGTT CTAAAGGTTT AAAATTAGAG TTTTACATT TGTTTGATGA	1490
	AAAAGGCCTT AAATTGAGT TTTCCCGTT GATTTGATGA AAAAGCCCTA	1540
15	GAATTGTGT TTTCCGTCG GTTTGATTCT GAAGGCCTAA AATTGAGTT	1590
	TCTCCGGCTG TTTTGATGAA AAAGCCCTAA ATTTGAGTTT CTCCGGCTGT	1640
20	TTTGATGAAA AAGCCCTAAA TTTGAAGTTT TTTCCCGTG TTTTAGATTG	1690
	TTTAGGTTTT AATTCTCGAA TCAGCTAATC AGGGAGTGTG AAAGCCCTAA	1740
	ATTGAAGTTT TTTTCGTTGT TCTGATTGTT GTTTTTATGA ATTTGCAG	1788
25	ATG CAG ATC TTT GTG AAA ACT CTC ACC GGA AAG ACT ATC ACC	1830
	Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr	
	1 5 10	
30	CTA GAG GTG GAA AGT TCT GAT ACA ATC GAC AAC GTT AAG GCT	1872
	Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn Val Lys Ala	
	15 20 25	
35	AAG ATC CAG GAT AAG GAA GGA ATT CCC CCG GAT CAG CAA AGG	1914
	Lys Ile Glu Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg	
	30 35 40	
40	CTT ATC TTC GCC GGA AAG CAG TTG GAG GAC GGA CGT ACT CTA	1956
	Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu	
	45 50 55	
	GCT GAT TAC AAC ATC CAG AAG GAG TCT ACC CTC CAT TTG GTG	1998
	Ala Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val	
	60 65 70	
45	CTC CGT CTA CGT GGA GGT GGA TCC GCT GTT AAA AGA GTG GGT	2040
	Leu Arg Leu Arg Gly Gly Gly Ser Ala Val Lys Arg Val Gly	
	75 80	
50	CGT AGG TTG AAA AAG TTG GAC CGT AAG ATT GAT AGG TTA GGA	2082
	Arg Arg Leu Lys Lys Leu Asp Arg Lys Ile Asp Arg Leu Gly	
	85 90 95	

	GTT GAT TTT TGATCTAGAG TCGACCGATC CCCC GAATTT CCCC GA	2127
	Val Asp Phe	
	100	
5	<u>SEQ ID NO 96</u>	
	TTTATCAATC AGATT TGAAC ATATAAATAA ATATAAATTG TCTCAATAAT	50
	TCTACATTAA ACTAATATTT GAAATCTCAA TTTTATGATT TTTTAAATTC	100
10	ACTTTATATC CAAGACAATT TNCANCTTCA AAAAGTTTTA TTAAANATTT	150
	ACATTAGTTT TGTTGATGAG GATGACAAGA TTTTGGTCAT CAATTACATA	200
	TACCCAAATT GAATAGTAAG CAACTTCAAT GTTTTTCATA ATGATAATGA	250
15	CAGACACAAN NNAACCCAT TTATTATICA CATTGATTGA GTTTTATATG	300
	CAATATAGTA ATAATAATAA TATTTCTTAT AAAGCAAGAG GTCAATTTTT	350
20	TTTAAATTAT ACCACGTCAC TAAATTATAT TTGATAATGT AAAACAATTC	400
	AAATTTTACT TAAATATCAT GAAATAAACT ATTTTATAA CCAAATTACT	450
	AAATTTTCC AATAAAAAA AGTCATTAAG AAGACATAAA ATAAATTGA	500
25	GGTAAANGAG TGAAGTCGAC TGACTTTTTT TTTTTTATC ATAAGAAAAT	550
	AAATTATTAA CTTTAACCTA ATAAACACT AATATAATTT CATGGAATCT	600
30	AATACTTACC TCTTAGAAAT AAGAAAAAGT GTTCTAATA GACCTCAAT	650
	TTACATTAAA TATTTTCAAT CAAATTTAAA TAACAAATAT CAATATGAGG	700
	TCAATAACAA TATCAAAATA ATATGAAAAA AGAGCAATAC ATAATATAAG	750
35	GGACGATTTA AGTGCGATTA TCAAGGTAGT ATTATATCCT AATTGCTAA	800
	TATTTGNGCT CTTATATTTA AGGTCATGTT CATGATAAAC TTGAAATGCG	850
40	CTATATTAGA GCATATATTA AAATAAAAAA ATACCTAAAA TAAAATTAAG	900
	TTATTTTTAG TATATATTTT TTTACATGAC CTACATTTTT CTGGGTTTTT	950
	CTAAAGGAGC GTGTAAGTGT CGACCTCAAT CTCCTAATTT TCCCCACCAC	1000
45	ATAAAAATTA AAAAGGAAAG GTAGCTTTTG CGTGTGTTTT TGGTACACTA	1050
	CACCTCATTA TTACACGTGT CCTCATATAA TTGGTTAACC CTATGAGGCG	1100
50	GTTCGTCTA GAGTCGGCCA TGCCATCTAT AAAATGAAGC TTTCTGCACC	1150
	TCATTTTTTT CATCTTCTAT CTGATTTCTA TTATAATTTT TCTCAATTGC	1200

	CTTCAAATTT CTCTTTAAGG TTAGAATCTT CTCTATTTTT	1240
	GGTTTTTGTA TGTTTAGATT CTCGAATTAG CTAATCAGGC GCTGTTATAG	1290
5	CCCTTCCTTT TGAGTCTCTC CTCGGTTGTC TTGATGGAAA AGGCCTAACA	1340
	TTTGAGTTTT TTTACGTC TGTTTGATGGA AAAGGCCTAC AATTGGCCGT	1390
10	TTTCCCCGTT CGTTTTGATG AAAAAGCCCC TAGTTTGAGA TTTTTTTTCT	1440
	GTCGTTTCGTT CTAAAGGTTT AAAATTAGAG TTTTACATT TGTTTGATGA	1490
	AAAAGGCCTT AAATTGAGT TTTTCCGGTT GATTTGATGA AAAAGCCCTA	1540
15	GAATTTGTGT TTTTCCGTG GTTTGATTCT GAAGGCCTAA AATTGAGTT	1590
	TCTCCGGCTG TTTTGATGAA AAAGCCCTAA ATTTGAGTTT CTCCGGCTGT	1640
20	TTTGATGAAA AAGCCCTAAA TTTGAAGTTT TTTCCCCGTG TTTTAGATTG	1690
	TTTAGGTTTT AATTCTCGAA TCAGCTAATC AGGGAGTGTG AAAGCCCTAA	1740
	ATTGAAGTTT TTTTCGTTGT TCTGATTGTT GTTTTATGA ATTTGCAG	1788
25	ATG CAG ATC TTT GTG AAA ACT CTC ACC GGA AAG ACT ATC ACC Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr 1 5 10	1830
30	CTA GAG GTG GAA AGT TCT GAT ACA ATC GAC AAC GTT AAG GCT Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn Val Lys Ala 15 20 25	1872
35	AAG ATC CAG GAT AAG GAA GGA ATT CCC CCG GAT CAG CAA AGG Lys Ile Glu Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg 30 35 40	1914
40	CTT ATC TTC GCC GGA AAG CAG TTG GAG GAC GGA CGT ACT CTA Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu 45 50 55	1956
	GCT GAT TAC AAC ATC CAG AAG GAG TCT ACC CTC CAT TTG GTG Ala Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val 60 65 70	1998
45	CTC CGT CTA CGT GGA GGT GGA TCC Leu Arg Leu Arg Gly Gly Gly Ser 75	2022

Example 4Construction of Ubiquitin-Lytic Peptide Fusion Gene Plasmid Vectors

5 pUC19 and pCGN1547 plasmid vectors containing a potato
(*Solanum tuberosum*) Ubi3 promoter, a region coding for a ubiquitin
polypeptide, and a gene coding for a lytic peptide are constructed
according to Example 2. Each plasmid respectively contains one
10 lytic peptide nucleotide sequence coding for an amino acid
sequence corresponding to SEQ ID NO. 1, 7, 15, 21, 30, 39, 43, 52,
83, 86, 88, 90, and 91. The resultant pUC19 Ubi3 ubiquitin-lytic
peptide recombinant plasmids are designated as follows: pUCUbi3-
LP1, pUCUbi3-LP7, pUCUbi3-LP15, pUCUbi3-LP21, pUCUbi3-LP30,
pUCUbi3-LP39, pUCUbi3-LP43, pUCUbi3-LP52, pUCUbi3-LP83, pUCUbi3-
15 LP86, pUCUbi3-LP88, pUCUbi3-LP90, and pUCUbi3-LP91. The resultant
pCGN1547 Ubi3 ubiquitin-lytic peptide recombinant plasmids are
designated as follows: pCGNUbi3-LP1, pCGNUbi3-LP7, pCGNUbi3-LP15,
pCGNUbi3-LP21, pCGNUbi3-LP30, pCGNUbi3-LP39, pCGNUbi3-LP43,
pCGNUbi3-LP52, pCGNUbi3-LP83, pCGNUbi3-LP86, pCGNUbi3-LP88,
20 pCGNUbi3-LP90, and pCGNUbi3-LP91.

 pUC19 and pCGN1547 plasmid vectors containing a potato
(*Solanum tuberosum*) Ubi7 promoter and intron, a region coding for
a ubiquitin polypeptide, and a gene coding for a lytic peptide are
constructed according to Example 3. Each plasmid respectively
25 contains one lytic peptide nucleotide sequence coding for an amino
acid sequence corresponding to SEQ ID NO. 1, 7, 15, 21, 30, 39,
43, 52, 83, 85, 88, 90, and 91. The resultant pUC19 Ubi7
ubiquitin-lytic peptide recombinant plasmids are designated as
follows: pUCUbi7-LP1, pUCUbi7-LP7, pUCUbi7-LP15, pUCUbi7-LP21,
30 pUCUbi7-LP30, pUCUbi7-LP39, pUCUbi7-LP43, pUCUbi7-LP52, pUCUbi7-
LP83, pUCUbi7-LP86, pUCUbi7-LP88, pUCUbi7-LP90, and pUCUbi7-LP91.
The resultant pCGN1547 Ubi7 ubiquitin-lytic peptide recombinant
plasmids are designated as follows: pCGNUbi7-LP1, pCGNUbi7-LP7,
pCGNUbi7-LP15, pCGNUbi7-LP21, pCGNUbi7-LP30, pCGNUbi7-LP39,
35 pCGNUbi7-LP43, pCGNUbi7-LP52, pCGNUbi7-LP83, pCGNUbi7-LP86,
pCGNUbi7-LP88, pCGNUbi7-LP90, and pCGNUbi7-LP91.

Example 5Construction of GUS-Ubiquitin Fusion Gene Recombinant DNA Molecules and Ubiquitin Promoter-GUS Recombinant DNA Molecules

5

Two chimeric genes containing a β -glucuronidase (GUS) reporter gene and the Ubi3 promoter were constructed in pCGN1547 plasmid vectors according to Garbarino, J., and Belknap, W., Plant Molecular Biology 24: 119 (1994), hereby incorporated by reference in its entirety. The first vector contains the 920 bp Ubi3 promoter ligated to the GUS gene, and expresses the GUS protein. This plasmid is designated pCGNUbi3-GUS. The second vector contains the 920 bp Ubi3 promoter and 228 bp ubiquitin coding region ligated in frame to the GUS gene. This plasmid expresses a ubiquitin-GUS fusion polypeptide. This plasmid is designated pCGNUbi3-GUSf.

Two chimeric genes containing a β -glucuronidase (GUS) reporter gene and the Ubi7 promoter minus the intron region were constructed in pCGN1547 plasmid vectors using PCR, as described in Example 3 and in Garbarino, J., and Belknap, W., Plant Molecular Biology 24: 119 (1994). The first vector contains a 1156 bp Ubi7 promoter region insert, including the 5' untranslated region of ubiquitin, ligated to the GUS gene. This plasmid does not contain the Ubi7 intron and expresses the GUS protein. This plasmid is designated pCGNUbi7-GUS. The second vector contains the 1156 Ubi7 ubiquitin promoter from pCGNUbi7-GUS and the 228 bp ubiquitin coding region fused in frame to the GUS reporter gene. This plasmid expresses a ubiquitin-GUS fusion polypeptide and is designated pCGNUbi7-GUSf.

30

Example 6Plant Transformation and GUS Gene Expression

The chimeric plasmids pCGNUbi3-GUS, pCGNUbi3-GUSf, pCGNUbi7-GUS, and pCGNUbi7-GUSf from Example 5 are introduced into the potato (*Solanum tuberosum*) using *Agrobacterium* mediated

35

- transformation according to Garbarino, J., and Belknap, W. *Plant Molecular Biology* 24:119 (1994). The strain of *Agrobacterium tumefaciens* used for transformation (PC2760, see An, G., et al., *EMBO J.* 4: 277 (1985)) harbors the disarmed Ti plasmid pAL4404
- 5 (see Hoekema, A., et al., *Nature* 303: 179 (1983)). Plant transformation is carried out as previously described in Synder, G.W., et al., *Plant Cell Rep* 12:324 (1993), except that 1 mg/l silver thiosulfate is added to the stage II transformation medium (see Chang, H.H., et al., *Bot Bull Acad Sci* 32: 63 (1991)).
- 10 Expression of the ubiquitin-GUS fusion polypeptide and mRNA products and the GUS protein alone is examined by northern and western analysis, as described in Garbarino J., and Belknap, W., *Plant Molecular Biology* 24: 119 (1994). GUS protein expression is examined in the transgenic plants using western analysis.
- 15 Although there is a wide range of activity among individual clones, the ubiquitin-GUS fusion polypeptide containing plants generally give 5-10 fold higher expression than the plants containing GUS protein alone. This higher level of protein expression corresponds to similarly elevated mRNA transcription
- 20 levels for the ubiquitin-GUS fusion constructs, as shown by northern analysis (described in Garbarino et al., *Plant Molecular Biology* 24: 119 (1994)). Western analysis also shows that the ubiquitin-GUS fusion polypeptide was appropriately processed by endogenous ubiquitin hydrolases to produce free GUS protein.
- 25 GUS protein activity is measured as described by Jefferson, R.A., et al., *EMBO J.* 6: 3901 (1987). Table 4 below shows a comparison of the GUS activities in plants transformed with pCGNubi3-GUS (ubi-) and plants transformed with pCGNubi3-GUSf (ubi+). The activity is measured in nmoles methyl umbelliferon
- 30 (MU) per minute per milligram of protein. Methyl umbelliferon is the fluorescent product of the GUS enzymatic reaction.

TABLE 4: COMPARISON OF GUS PROTEIN ACTIVITY IN PLANTS TRANSFORMED WITH THE UBI3 PROMOTER WITH (+UBI) AND WITHOUT (-UBI) UBIQUITIN POLYPEPTIDE FUSION

Construct	GUS Activity (nmoles MU/min/mg protein)				
	Leaf Meristem	2nd Leaf	5th Leaf	Senescent Leaf	Tuber
3.2-ubi	6.31±0.74	2.51±0.52	1.79±0.22	5.42±1.24	3.26±0.27
8.1-ubi	25.8±2.08	9.98±2.10	6.34±1.00	19.20±6.11	14.2±1.6
3.5+ubi	94.8±12.6	60.3±25.1	32.7±8.71	50.1±11.6	37.6±10.4
9.8+ubi	33.3±0.5	18.9±2.75	9.74±0.99	22.7±3.57	20.7±3.45

5

Example 7

Plant Transformation and Ubiquitin-Lytic Peptide Gene Expression

The chimeric plasmids pCGNubi3-LP98 from Example 2 and
 10 pCGNubi7-LP98 from Example 3 are introduced into the potato (*Solanum tuberosum*) using *Agrobacterium* mediated transformation according to Garbarino, J., and Belknap, W. Plant Molecular Biology 24:119 (1994). The strain of *Agrobacterium tumefaciens* used for transformation (PC2760, see An, G., et al., EMBO J. 4:
 15 277 (1985)) harbors the disarmed Ti plasmid pAL4404 (see Hoekema, A., et al., Nature 303: 179 (1983). Plant transformation is carried out as previously described in Synder, G.W., et al., Plant Cell Rep 12:324 (1993), except that 1 mg/l silver thiosulfate is added to the stage II transformation medium (see Chang, H.H., et
 20 al., Bot Bull Acad Sci 32: 63 (1991).

Expression of the ubiquitin-lytic peptide fusion polypeptide and mRNA products is examined by northern and western analysis, as described in Example 6 and Garbarino J., and Belknap, W., Plant Molecular Biology 24: 119 (1994). Northern analysis shows that
 25 ubiquitin-lytic peptide mRNA is transcribed from the gene construct in the transgenic plants. Western analysis shows that the ubiquitin-lytic peptide fusion polypeptide is appropriately

processed by endogenous ubiquitin hydrolases to produce free lytic peptide.

Example 8

Cloned Ubi3/Ubi7 Promoter Activity

5

mRNA expression from the cloned Ubi3 promoter was examined before and after wounding to determine if the cloned Ubi3 promoter is wound inducible in transformed plants (see Garbarino, J. and
10 Belknap, W., Plant Molecular Biology 24:119 (1994)). Northern analysis comparing endogenous Ubi3 mRNA expression levels to pCGNUbi3-GUS and pCGNUbi3-GUSf mRNA expression levels in transformed plants (see Example 5) shows that while the endogenous Ubi3 mRNA transcription increases upon wounding, transcription
15 from the recombinant Ubi3 plasmids does not. Thus the recombinant Ubi3 promoter does not have the wound inducible characteristic of the endogenous Ubi3 promoter. This result suggests that the 920 bp of upstream sequence cloned in the Ubi3 genomic clone is not sufficient to obtain wound-dependent activation of the promoter.
20 The promoter instead is constitutive, however, it still demonstrates developmental regulation, as shown in Table 4 above.

In contrast, the cloned Ubi7 promoter retains its wound-dependent induction. Northern analysis comparing the endogenous Ubi7 mRNA expression levels to the expression levels from
25 pCGNUbi7-GUS and pCGNUbi7-GUSf in transformed plants (see Example 5) shows that both the endogenous and the cloned Ubi7 promoter have wound-dependent activation.

DEPOSIT INFORMATION

5 E. coli cultures, each respectively transformed with pUCUbi7-
LP98 (Local Accession No. PBT-0273), pUCUbi3-LP98 (Local Accession
No. PBT-0276), pUCUbi7 (Local Accession No. PBT-0277), and pUCUbi3
(Local Accession No. PBT-0234) were deposited in the Agricultural
Research Service Culture Collection (NRRL). The depository is
located at located at 1815 North University Street, Peoria, IL,
10 61604.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

- (A) NAME: DEMETER BIOTECHNOLOGIES, LTD.
- (B) STREET: 905 W. MAIN ST., BRIGHTLEAF SQUARE STE 19-D
- (C) CITY: DURHAM
- (D) STATE: NORTH CAROLINA
- (E) COUNTRY: USA
- (F) POSTAL CODE (ZIP): 27701
- (G) TELEPHONE: (919) 682-7181
- (H) TELEFAX: (919) 682-8340

(i) APPLICANT:

- (A) NAME: UNITED STATES OF AMERICA, AS REPRESENTED BY
THE SECRETARY OF AGRICULTURE
- (B) STREET:
- (C) CITY: WASHINGTON
- (D) STATE: D. C.
- (E) COUNTRY: USA
- (F) POSTAL CODE (ZIP): 20250-1400
- (G) TELEPHONE:
- (H) TELEFAX:

(ii) TITLE OF INVENTION: UBIQUITIN-LYTIC PEPTIDE FUSION GENE
CONSTRUCTS, PROTEIN PRODUCTS DERIVING THEREFROM, AND
METHODS OF MAKING AND USING THE SAME

(iii) NUMBER OF SEQUENCES: 98

(iv) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Floppy disk
- (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: WORDPERFECT 5.1+

(v) CURRENT APPLICATION DATA:

- (A) APPLICATION NUMBER:
- (B) FILING DATE: 21-JUL-1994

(vi) PRIOR APPLICATION DATA: 08/279,472

- (A) APPLICATION NUMBER: 08/279,472
- (B) FILING DATE: 22-JUL-1994

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
 1 5 10 15

Lys Ala Val Lys Lys Ala Val Lys Lys Lys Lys
 20 25

(3) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2

Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Lys Lys Ala
 1 5 10 15

Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala Val Lys Lys Lys Lys
 20 25 30

(4) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3

Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Ala Val Lys
 1 5 10 15

Ala Val Lys Lys Ala Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala
 20 25 30

Val Lys Lys Lys Lys
 35

(5) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
 1 5 10 15

Lys Ala Val Lys Lys Ala Val
 20

(6) INFORMATION FOR SEQ ID NO: 5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5

Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Lys Lys Ala
 1 5 10 15
 Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala Val
 20 25

(7) INFORMATION FOR SEQ ID NO: 6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6

Phe Ala Val Ala Val Lys Ala Val Ala Val Lys Ala Val Ala Val Lys
 1 5 10 15
 Ala Val Lys Lys Ala Val Lys Lys Val Lys Lys Ala Val Lys Lys Ala
 20 25 30
 Val

(8) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
1 5 10 15

Arg Gly Val Arg Lys Val Ala Lys Arg Lys Arg
20 25

(9) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
1 5 10 15

Arg Gly Val Arg Lys Val Ala
20

- (10) INFORMATION FOR SEQ ID NO: 9:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
 - (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
 - (iii) HYPOTHETICAL: NO
 - (v) FRAGMENT TYPE: COMPLETE PEPTIDE
 - (vi) ORIGINAL SOURCE: SYNTHETIC
 - (vii) IMMEDIATE SOURCE: SYNTHETIC
 - (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9

Lys Arg Lys Arg Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu
1 5 10 15
Ala Arg Lys Ile Ala Arg Leu Gly Val Ala Phe
20 25

- (11) INFORMATION FOR SEQ ID NO: 10:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
 - (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
 - (iii) HYPOTHETICAL: NO
 - (v) FRAGMENT TYPE: COMPLETE PEPTIDE
 - (vi) ORIGINAL SOURCE: SYNTHETIC
 - (vii) IMMEDIATE SOURCE: SYNTHETIC
 - (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10

Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu Ala Arg Lys Ile
1 5 10 15
Ala Arg Leu Gly Val Ala Phe
20

(12) INFORMATION FOR SEQ ID NO: 11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 31
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
 1 5 10 15
 Arg Gly Val Arg Lys Val Ala Lys Arg Lys Arg Lys Lys Asp Leu
 20 25 30

(13) INFORMATION FOR SEQ ID NO: 12:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 26
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12

Phe Ala Val Gly Leu Arg Ala Ile Lys Arg Ala Leu Lys Lys Leu Arg
 1 5 10 15
 Arg Gly Val Arg Lys Val Ala Lys Asp Leu
 20 25

(i) SEQUENCE CHARACTERISTICS:

- ```

1) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30
 (B) TYPE: AMINO ACID
 (C) TOPOLOGY: LINEAR
(ii) MOLECULE TYPE:
 (A) DESCRIPTION: PEPTIDE
(iii) HYPOTHETICAL: NO
(v) FRAGMENT TYPE: COMPLETE PEPTIDE
(vi) ORIGINAL SOURCE: SYNTHETIC
(vii) IMMEDIATE SOURCE: SYNTHETIC
(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13

```

Lys Arg Lys Arg Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu  
1 5 10 15

Ala Arg Lys Ile Ala Arg Leu Gly Val Ala Phe Lys Asp Leu  
20 25 30

(i) SEQUENCE CHARACTERISTICS:

- ```

(ii) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 26
    (B) TYPE: AMINO ACID
    (C) TOPOLOGY: LINEAR
(iii) MOLECULE TYPE:
    (A) DESCRIPTION: PEPTIDE
(iv) HYPOTHETICAL: NO
(v) FRAGMENT TYPE: COMPLETE PEPTIDE
(vi) ORIGINAL SOURCE: SYNTHETIC
(vii) IMMEDIATE SOURCE: SYNTHETIC
(viii) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
(ix) SEQUENCE DESCRIPTION: SEQ ID NO: 14

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Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu Ala Arg Lys Ile
1 5 10 15

Ala Arg Leu Gly Val Ala Phe Lys Asp Leu
20 25

(16) INFORMATION FOR SEQ ID NO: 15:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15
 Ala Lys Lys Val Ala Lys Val Ala Val Ala Val
 20 25

(17) INFORMATION FOR SEQ ID NO: 16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 32
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15
 Ala Lys Lys Val Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Val
 20 25 30

(18) INFORMATION FOR SEQ ID NO: 17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 37
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15
 Ala Lys Lys Val Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Lys
 20 25 30
 Val Ala Val Ala Val
 35

(19) INFORMATION FOR SEQ ID NO: 18:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18

Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val Ala Lys Lys Val
 1 5 10 15
 Ala Lys Val Ala Val Ala Val
 20

(20) INFORMATION FOR SEQ ID NO: 19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19

Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val Ala Lys Lys Val
 1 5 10 15

Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Val
 20 25

(21) INFORMATION FOR SEQ ID NO: 20:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20

Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val Ala Lys Lys Val
 1 5 10 15

Ala Lys Val Ala Val Ala Lys Val Ala Val Ala Lys Val Ala Val Ala
 20 25 30

Val

(22) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val
 1 5 10 15
 Ala Lys Val Ala Lys Lys Val Ala Lys Lys Val
 20 25

(23) INFORMATION FOR SEQ ID NO: 22:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 32
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val
 1 5 10 15
 Ala Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala
 20 25 30

(24) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23

Lys Lys Lys Lys Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val
1 5 10 15

Ala Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala
20 25 30

Lys Val Ala Lys Lys
35

(25) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
1 5 10 15

Lys Lys Val Ala Lys Lys Val
20

(26) INFORMATION FOR SEQ ID NO: 25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15

Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala
 20 25

(27) INFORMATION FOR SEQ ID NO: 26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15

Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Val Ala Lys
 20 25 30

Lys

(28) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
1 5 10 15

Lys Lys Val Ala Lys Lys Val Lys Lys Lys Lys
20 25

(29) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
1 5 10 15

Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Lys Lys Lys
20 25 30

(30) INFORMATION FOR SEQ ID NO: 29:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 37
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29

Phe Val Lys Lys Val Ala Lys Val Ala Lys Lys Val Ala Lys Val Ala
 1 5 10 15

Lys Lys Val Ala Lys Lys Val Ala Lys Lys Val Ala Lys Val Ala Lys
 20 25 30

Lys Lys Lys Lys Lys
 35

(31) INFORMATION FOR SEQ ID NO: 30:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Lys Lys Lys Lys
 1 5 10 15

(32) INFORMATION FOR SEQ ID NO: 31:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15
Ala Lys Lys Lys Lys
20

(33) INFORMATION FOR SEQ ID NO: 32:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15
Ala Lys Val Lys Ala Lys Val Lys Lys Lys Lys
20 25

- (34) INFORMATION FOR SEQ ID NO: 33:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 12
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
 - (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
 - (iii) HYPOTHETICAL: NO
 - (v) FRAGMENT TYPE: COMPLETE PEPTIDE
 - (vi) ORIGINAL SOURCE: SYNTHETIC
 - (vii) IMMEDIATE SOURCE: SYNTHETIC
 - (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10

- (35) INFORMATION FOR SEQ ID NO: 34:
- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
 - (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
 - (iii) HYPOTHETICAL: NO
 - (v) FRAGMENT TYPE: COMPLETE PEPTIDE
 - (vi) ORIGINAL SOURCE: SYNTHETIC
 - (vii) IMMEDIATE SOURCE: SYNTHETIC
 - (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15

Ala

(36) INFORMATION FOR SEQ ID NO: 35:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35

Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15

Ala Lys Val Lys Ala Lys Val
20

(37) INFORMATION FOR SEQ ID NO: 36:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36

Lys Lys Lys Lys Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15

(38) INFORMATION FOR SEQ ID NO: 37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37

Lys Lys Lys Lys Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15

Ala Lys Val Lys Ala
20

(39) INFORMATION FOR SEQ ID NO: 38:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38

Lys Lys Lys Lys Phe Lys Val Lys Ala Lys Val Lys Ala Lys Val Lys
1 5 10 15

Ala Lys Val Lys Ala Lys Val Lys Ala Lys Val
20 25

(40) INFORMATION FOR SEQ ID NO: 39:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 25
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39

Phe Lys Lys Val Lys Lys Val Ala Lys Lys Val Cys Lys Cys Val Lys
 1 5 10 15

Lys Ala Val Lys Lys Val Lys Lys Phe
 20 25

(41) INFORMATION FOR SEQ ID NO: 40:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
 1 5 10 15

Lys Ala Val Lys Lys Ala Val Cys Cys Cys Cys
 20 25

(42) INFORMATION FOR SEQ ID NO: 41:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41

Cys Cys Cys Cys Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15

Ala Lys Lys Val Ala Lys Val Ala Val Ala Val
 20 25

(43) INFORMATION FOR SEQ ID NO: 42:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42

Phe Ala Val Ala Val Lys Ala Val Lys Lys Ala Val Lys Lys Val Lys
 1 5 10 15

Lys Ala Val Lys Lys Ala Val Ser Ser Ser Ser
 20 25

(44) INFORMATION FOR SEQ ID NO: 43:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43

Ser Ser Ser Ser Phe Val Lys Lys Val Ala Lys Lys Val Lys Lys Val
 1 5 10 15

Ala Lys Lys Val Ala Lys Val Ala Val Ala Val
 20 25

(45) INFORMATION FOR SEQ ID NO: 44:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44

Phe Ala Leu Ala Leu Lys Ala Leu Lys Lys Ala Leu Lys Lys Leu Lys
 1 5 10 15

Lys Ala Leu Lys Lys Ala Leu
 20

(46) INFORMATION FOR SEQ ID NO: 45:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45

Leu Ala Lys Lys Leu Ala Lys Lys Leu Lys Lys Leu Ala Lys Lys Leu
1 5 10 15

Ala Lys Leu Ala Leu Ala Phe
20

(47) INFORMATION FOR SEQ ID NO: 46:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46

Phe Ala Phe Ala Phe Lys Ala Phe Lys Lys Ala Phe Lys Lys Phe Lys
1 5 10 15

Lys Ala Phe Lys Lys Ala Phe
20

(48) INFORMATION FOR-SEQ ID NO: 47:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47

Phe Ala Ile Ala Ile Lys Ala Ile Lys Lys Ala Ile Lys Lys Ile Lys
1 5 10 15

Lys Ala Ile Lys Lys Ala Ile
20

(49) INFORMATION FOR SEQ ID NO: 48:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48

Phe Ala Lys Lys Phe Ala Lys Lys Phe Lys Lys Phe Ala Lys Lys Phe
1 5 10 15

Ala Lys Phe Ala Phe Ala Phe
20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17
(B) TYPE: AMINO ACID
(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49

Phe Lys Arg Leu Ala Lys Ile Lys Val Leu Arg Leu Ala Lys Ile Lys
1 5 10 15

Arg

(51) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37
(B) TYPE: AMINO ACID
(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50

Lys Leu Lys Leu Ala Val Lys Leu Val Gly Leu Leu Arg Lys Lys Arg
1 5 10 15

Ala Leu Lys Ile Ala Leu Arg Gly Val Ala Lys Arg Ala Gly Arg Leu
20 25 30

Ala Val Arg Lys Phe
35

(54) INFORMATION FOR SEQ ID NO: 53:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53

Phe Ala Val Ala Val Ser Ala Val Ser Ser Ala Val Ser Ser Val Ser
1 5 10 15
Ser Ala Val Ser Ser Ala Val
20

(55) INFORMATION FOR SEQ ID NO: 54:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54

Phe Ala Val Ala Val Ser Ala Val Ser Ser Ala Val Ser Ser Val Ser
1 5 10 15
Ser Ala Val Ser Ser Ala Val Ser Ser Ser Ser
20 25

(56) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55

Phe Ala Lys Lys Phe Ala Lys Lys Phe Lys Lys Phe Ala Lys Lys Phe
1 5 10 15

1

5

10

15

Ala Lys Phe Ala Phe Ala Phe Lys Lys Lys Lys
20 25

20

25

(57) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56

Lys Lys Lys Lys Phe Ala Lys Lys Phe Ala Lys Lys Phe Lys Lys Phe
1 5 10 15

1

5

10

15

Ala Lys Lys Phe Ala Lys Phe Ala Phe Ala Phe
20 25

20

25

(i) SEQUENCE CHARACTERISTICS:

- ```

17, (A) LENGTH: 23
 (B) TYPE: AMINO ACID
 (C) TOPOLOGY: LINEAR
(ii) MOLECULE TYPE:
 (A) DESCRIPTION: PEPTIDE
(iii) HYPOTHETICAL: NO
(v) FRAGMENT TYPE: COMPLETE PEPTIDE
(vi) ORIGINAL SOURCE: SYNTHETIC
(vii) IMMEDIATE SOURCE: SYNTHETIC
(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57

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Phe Ala Arg Lys Phe Leu Lys Arg Phe Lys Lys Phe Val Arg Lys Phe  
1 5 10 15

Ile Arg Phe Ala Phe Leu Phe  
20

(i) SEQUENCE CHARACTERISTICS:

- ```

      (A) LENGTH: 27
      (B) TYPE: AMINO ACID
      (C) TOPOLOGY: LINEAR
(ii) MOLECULE TYPE:
      (A) DESCRIPTION: PEPTIDE
(iii) HYPOTHETICAL: NO
(v) FRAGMENT TYPE: COMPLETE PEPTIDE
(vi) ORIGINAL SOURCE: SYNTHETIC
(vii) IMMEDIATE SOURCE: SYNTHETIC
(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58

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Phe Ala Arg Lys Phe Leu Lys Arg Phe Lys Lys Phe Val Arg Lys Phe
1 5 10 15

Ile Arg Phe Ala Phe Leu Phe Lys Arg Lys Arg
20 25

(60) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59

Lys Arg Lys Arg Phe Ala Arg Lys Phe Leu Lys Arg Phe Lys Lys Phe
 1 5 10 15

Val Arg Lys Phe Ile Arg Phe Ala Phe Leu Phe
 20 25

(61) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60

Ile Ala Lys Lys Ile Ala Lys Lys Ile Lys Lys Ile Ala Lys Lys Ile
 1 5 10 15

Ala Lys Ile Ala Ile Ala Ile
 20

(i) SEQUENCE CHARACTERISTICS:

- Ile Ala Lys Lys Ile Ala Lys Lys Ile Lys Lys Ile Ala Lys Lys Ile
1 5 10 15
Ala Lys Ile Ala Ile Ala Ile Lys Lys Lys Lys
20 25

(i) SEQUENCE CHARACTERISTICS:

- Lys Lys Lys Lys Ile Ala Lys Lys Ile Ala Lys Lys Ile Lys Lys Ile
 1 5 10 15
 Ala Lys Lys Ile Ala Lys Ile Ala Ile Ala Ile
 20 25

(64) INFORMATION FOR SEQ ID NO: 63:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63

Ile Ala Arg Lys Ile Leu Lys Arg Ile Lys Lys Ile Val Arg Lys Phe
1 5 10 15

Ile Arg Ile Ala Ile Leu Ile
20

(65) INFORMATION FOR SEQ ID NO: 64:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64

Ile Ala Arg Lys Ile Leu Lys Arg Ile Lys Lys Ile Val Arg Lys Phe
1 5 10 15

Ile Arg Ile Ala Ile Leu Ile Lys Arg Lys Arg
20 25

(66) INFORMATION FOR SEQ ID NO: 65:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65

Lys Arg Lys Arg Ile Ala Arg Lys Ile Leu Lys Arg Ile Lys Lys Ile
 1 5 10 15

Val Arg Lys Phe Ile Arg Ile Ala Ile Leu Ile
 20 25

(67) INFORMATION FOR SEQ ID NO: 66:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15

Leu

(68) INFORMATION FOR SEQ ID NO: 67:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67

Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
1 5 10 15

Ala Lys Ile Lys Leu
20

(69) INFORMATION FOR SEQ ID NO: 68:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
1 5 10 15

Leu Lys Arg Lys Arg
20

(70) INFORMATION FOR SEQ ID NO: 69:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
1 5 10 15

Leu Arg Val Lys Leu Lys Ile
20

(71) INFORMATION FOR SEQ ID NO: 70:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
1 5 10 15

Leu Arg Val Lys Leu Lys Ile Lys Arg Lys Arg
20 25

(72) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71

Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
 1 5 10 15

Ala Lys Ile Lys Leu Arg Val Lys Leu Lys Ile
 20 25

(73) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
 1 5 10 15

Leu Arg Val Lys Leu Lys Ile Arg Ala Arg Ile Lys Leu
 20 25

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
1 5 10 15

Leu Arg Val Lys Leu Lys Ile Arg Ala Arg Ile Lys Leu Lys Arg Lys
20 25 30

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(75) INFORMATION FOR SEQ ID NO: 74:
      (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 33
            (B) TYPE: AMINO ACID
            (C) TOPOLOGY: LINEAR
      (ii) MOLECULE TYPE:
            (A) DESCRIPTION: PEPTIDE
      (iii) HYPOTHETICAL: NO
      (v) FRAGMENT TYPE: COMPLETE PEPTIDE
      (vi) ORIGINAL SOURCE: SYNTHETIC
      (vii) IMMEDIATE SOURCE: SYNTHETIC
      (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
      (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74
```

Leu

(76) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
1 5 10 15

Leu Val Phe Ala Ile Leu Leu
20

(77) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76

Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg Ala Lys Ile Lys
1 5 10 15

Leu Val Phe Ala Ile Leu Leu Lys Arg Lys Arg
20 25

(78) INFORMATION FOR SEQ ID NO: 77:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77

Lys Arg Lys Arg Phe Lys Leu Arg Ala Lys Ile Lys Val Arg Leu Arg
 1 5 10 15

Ala Lys Ile Lys Leu Val Phe Ala Ile Leu Leu
 20 25

(79) INFORMATION FOR SEQ ID NO: 78:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 23
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78

Val Phe Ala Ile Leu Leu Phe Lys Leu Arg Ala Lys Ile Lys Val Arg
 1 5 10 15

Leu Arg Ala Lys Ile Lys Leu
 20

(80) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79

Val Phe Ala Ile Leu Leu Phe Lys Leu Arg Ala Lys Ile Lys Val Arg
1 5 10 15

Leu Arg Ala Lys Ile Lys Leu Lys Arg Lys Arg
20 25

(81) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27

(B) TYPE: AMINO ACID

(C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80

Lys Arg Lys Arg Val Phe Ala Ile Leu Leu Phe Lys Leu Arg Ala Lys
1 5 10 15

Ile Lys Val Arg Leu Arg Ala Lys Ile Lys Leu
20 25

(82) INFORMATION FOR SEQ ID NO: 81:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81

Val Gly Glu Cys Val Arg Gly Arg Cys Pro Ser Gly Met Cys Cys Ser
 1 5 10 15

Gln Phe Gly Tyr Cys Gly Lys Gly Pro Lys Tyr Cys Gly
 20 25

(83) INFORMATION FOR SEQ ID NO: 82:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82

Val Gly Glu Cys Val Arg Gly Arg Cys Pro Ser Gly Met Cys Cys Ser
 1 5 10 15

Gln Phe Gly Tyr Cys Gly Lys Gly Pro Lys Tyr Cys Gly Arg
 20 25 30

(84) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83

Leu Gly Asp Cys Leu Lys Gly Lys Cys Pro Ser Gly Met Cys Cys Ser
 1 5 10 15

Asn Tyr Gly Phe Cys Gly Arg Gly Pro Arg Phe Cys Gly Lys
 20 25 30

(85) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37
- (B) TYPE: AMINO ACID
- (C) TOPOLOGY: LINEAR

(ii) MOLECULE TYPE:

- (A) DESCRIPTION: PEPTIDE

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: COMPLETE PEPTIDE

(vi) ORIGINAL SOURCE: SYNTHETIC

(vii) IMMEDIATE SOURCE: SYNTHETIC

(x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84

Gln Cys Ile Gly Asn Gly Gly Arg Cys Asn Glu Asn Val Gly Pro Pro
 1 5 10 15

Tyr Cys Cys Ser Gly Phe Cys Leu Arg Gln Pro Gly Gln Gly Tyr Gly
 20 25 30

Tyr Cys Lys Asn Arg
 35

(86) INFORMATION FOR SEQ ID NO: 85:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 36
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85

Cys Ile Gly Asn Gly Gly Arg Cys Asn Glu Asn Val Gly Pro Pro Tyr
 1 5 10 15

Cys Cys Ser Gly Phe Cys Leu Arg Gln Pro Asn Gln Gly Tyr Gly Val
 20 25 30

Cys Arg Asn Arg
 35

(87) INFORMATION FOR SEQ ID NO: 86:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 36
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86

Cys Ile Gly Gln Gly Gly Lys Cys Gln Asp Gln Leu Gly Pro Pro Phe
 1 5 10 15

Cys Cys Ser Gly Tyr Cys Val Lys Asn Pro Gln Asn Gly Phe Gly Leu
 20 25 30

Cys Lys Gln Lys
 35

(88) INFORMATION FOR SEQ ID NO: 87:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 44
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87

Gln Lys Leu Cys Glu Arg Pro Ser Gly Thr Trp Ser Gly Val Cys Gly
 1 5 10 15
 Asn Asn Asn Ala Cys Lys Asn Gln Cys Ile Asn Leu Glu Lys Ala Arg
 20 25 30
 His Gly Ser Cys Asn Tyr Val Phe Pro Ala His Lys
 35 40

(89) INFORMATION FOR SEQ ID NO: 88:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 44
 - (B) TYPE: AMINO ACID
 - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
 - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88

Gln Arg Val Cys Asp Lys Pro Ser Gly Thr Trp Ser Gly Leu Cys Gly
 1 5 10 15
 Asn Asn Asn Ala Cys Arg Gln Asn Cys Ile Gln Val Asp Arg Ala Lys
 20 25 30
 Lys Gly Ser Cys Gln Phe Leu Tyr Pro Ala Lys Lys
 35 40

```
(90) INFORMATION FOR SEQ ID NO: 89:
      (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 36
            (B) TYPE: AMINO ACID
            (C) TOPOLOGY: LINEAR
      (ii) MOLECULE TYPE:
            (A) DESCRIPTION: PEPTIDE
      (iii) HYPOTHETICAL: NO
      (v) FRAGMENT TYPE: COMPLETE PEPTIDE
      (vi) ORIGINAL SOURCE: SYNTHETIC
      (vii) IMMEDIATE SOURCE: SYNTHETIC
      (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
      (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89
```

Gln Lys Leu Cys Gln Arg Pro Ser Gly Thr Trp Ser Gly Val Cys Gly
1 5 10 15
Asn Asn Asn Ala Cys Lys Asn Gln Cys Ile Arg Leu Glu Lys Ala Arg
20 25 30
His Gly Ser Cys
35

```
(91) INFORMATION FOR SEQ ID NO: 90:
      (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 36
            (B) TYPE: AMINO ACID
            (C) TOPOLOGY: LINEAR
      (ii) MOLECULE TYPE:
            (A) DESCRIPTION: PEPTIDE
      (iii) HYPOTHETICAL: NO
      (v) FRAGMENT TYPE: COMPLETE PEPTIDE
      (vi) ORIGINAL SOURCE: SYNTHETIC
      (vii) IMMEDIATE SOURCE: SYNTHETIC
      (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
      (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90
```

Gln Arg Val Cys Asn Lys Pro Ser Gly Thr Trp Ser Gly Leu Cys Gly
1 5 10 15
Asn Asn Asn Ala Cys Arg Gln Asn Cys Ile Lys Val Asp Arg Ala Lys
20 25 30
Lys Gly Ser Cys
35

(92) INFORMATION FOR SEQ ID NO: 91:

- ```
(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20
 (B) TYPE: AMINO ACID
 (C) TOPOLOGY: LINEAR
(ii) MOLECULE TYPE:
 (A) DESCRIPTION: PEPTIDE
(iii) HYPOTHETICAL: NO
(iv) FRAGMENT TYPE: COMPLETE PEPTIDE
(v) ORIGINAL SOURCE: SYNTHETIC
(vi) IMMEDIATE SOURCE: SYNTHETIC
(vii) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
(viii) SEQUENCE DESCRIPTION: SEQ ID NO: 91
```

Met Leu Glu Glu Leu Phe Glu Glu Met Thr Glu Phe Ile Glu Glu Val  
1 5 10 15  
Ile Glu Thr Met  
20

(93) INFORMATION FOR SEQ ID NO: 92:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1228  
(B) TYPE: NUCLEIC ACID  
(C) STRANDEDNESS: DOUBLE STRANDED  
(D) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:  
(A) DESCRIPTION: GENOMIC DNA AND OTHER NUCLEIC ACID
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92

|            |            |            |            |            |     |
|------------|------------|------------|------------|------------|-----|
| CCAAAGCACA | TACTTATCGA | TTTAAATTTC | ATCGAAGAGA | TTAATATCGA | 50  |
| ATAATCATAT | ACATACTTTA | AATACATAAC | AAATTTTTAA | TACATATATC | 100 |
| TGGTATATAA | TTAATTTTTT | AAAGTCATGA | AGTATGTATC | AAATACACAT | 150 |
| ATGGAAAAAA | TTAACTATTC | ATAATTTAAA | AAATAGAAAA | GATACATCTA | 200 |
| GTGAAATTAG | GTGCATGTAT | CAAATACATT | AGGAAAAGGG | CATATATCTT | 250 |
| GATCTAGATA | ATTAACGATT | TTGATTTATG | TATAATTTCC | AAATGAAGGT | 300 |
| TTATATCTAC | TTCAGAAATA | ACAATATACT | TTTATCAGAA | CATTCAACAA | 350 |
| AGCAACAACC | AACTAGAGTG | AAAAATACAC | ATTGTTCTCT | AGACATACAA | 400 |
| AATTGAGAAA | AGAATCTCAA | AATTTAGAGA | AACAAATCTG | AATTTCTAGA | 450 |
| AGAAAAAAAT | AATTATGCAC | TTTGCTATTG | CTCGAAAAAT | AAATGAAAGA | 500 |
| AATTAGACTT | TTTTAAAAGA | TGTTAGACTA | GATATACTCA | AAAGCTATTA | 550 |
| AAGGAGTAAT | ATTCTTCTTA | CATTAAGTAT | TTTAGTTACA | GTCCTGTAAT | 600 |

|                                                         |      |
|---------------------------------------------------------|------|
| TAAAGACACA TTTTAGATTG TATCTAAACT TAAATGTATC TAGAATACAT  | 650  |
| ATATTTGAAT GCATCATATA CATGTATCCG ACACACCAAT TCTCATAAAA  | 700  |
| AACGTAATAT CCTAAACTAA TTTATCCTTC AAGTCAACTT AAGCCCAATA  | 750  |
| TACATTTTCA TCTCTAAAGG CCCAAGTGGC ACAAATGTC AGGCCCAATT   | 800  |
| ACGAAGAAAA GGGCTTGTA AACCCTAATA AAGTGGCACT GGCAGAGCTT   | 850  |
| ACACTCTCAT TCCATCAACA AAGAAACCCT AAAAGCCGCA GCGCCACTGA  | 900  |
| TTTCTCTCCT CCAGGCGAAG ATG CAG ATC TTC GTG AAG ACC TTA   | 944  |
| Met Gln Ile Phe Val Lys Thr Leu                         |      |
| 1 5                                                     |      |
| ACG GGG AAG ACG ATC ACC CTA GAG GTT GAG TCT TCC GAC ACC | 986  |
| Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr |      |
| 10 15 20                                                |      |
| ATC GAC AAT GTC AAA GCC AAG ATC CAG GAC AAG GAA GGG ATT | 1028 |
| Ile Asp Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile |      |
| 25 30 35                                                |      |
| CCC CCA GAC CAG CAG CGT TTG ATT TTC GCC GGA AAG CAG CTT | 1070 |
| Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu |      |
| 40 45 50                                                |      |
| GAG GAT GGT CGT ACT CTT GCC GAC TAC AAC ATC CAG AAG GAG | 1112 |
| Glu Asp Gly Arg Thr Leu Ala Asp Tyr Asn Ile Gln Lys Glu |      |
| 55 60                                                   |      |
| TCA ACT CTC CAT CTC GTG CTC CGT CTC CGT GGT GGT         | 1148 |
| Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly         |      |
| 65 70 75                                                |      |
| GGA TCC GCT GTT AAA AGA GTG GGT CGT AGG TTG AAA AAG TTG | 1190 |
| Gly Ser Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu |      |
| 80 85 90                                                |      |
| GAC CGT AAG ATT GAT AGG TTA GGA GTT GAT TTT TGATC       | 1228 |
| Asp Arg Lys Ile Asp Arg Leu Gly Val Asp Phe             |      |
| 95 100                                                  |      |

## (94) INFORMATION FOR SEQ ID NO: 93:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1154

(B) TYPE: NUCLEIC ACID

(C) STRANDEDNESS: DOUBLE STRANDED

(D) TOPOLOGY: LINEAR

## (ii) MOLECULE TYPE:

(A) DESCRIPTION: GENOMIC DNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93

97

TCA ACT CTC CAT CTC GTG CTC CGT CTC CGT GGT GGT GGA TCC 1154  
 Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Gly Ser  
 65 70 75

## (95) INFORMATION FOR SEQ ID NO: 94:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 78

(B) TYPE: AMINO ACID

(D) TOPOLOGY: LINEAR

## (ii) MOLECULE TYPE:

(A) DESCRIPTION: PEPTIDE

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94

Met Gln Ile Phe Val Lys Thr Leu  
 1 5

Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr  
 10 15 20

Ile Asp Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile  
 25 30 35

Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu  
 40 45 50

Glu Asp Gly Arg Thr Leu Ala Asp Tyr Asn Ile Gln Lys Glu  
 55 60

Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Gly Ser  
 65 70 75

## (96) INFORMATION FOR SEQ ID NO: 95:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2127

(B) TYPE: NUCLEIC ACID

(C) STRANDEDNESS: DOUBLE STRANDED

(D) TOPOLOGY: LINEAR

## (ii) MOLECULE TYPE:

(A) DESCRIPTION: GENOMIC DNA AND OTHER DNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95

TTTATCAATC AGATTGGAAC ATATAAATAA ATATAAATTG TCTCAATAAT 50  
 TCTACATTAA ACTAATATTT GAAATCTCAA TTTTATGATT TTTTAAATTC 100  
 ACTTTATATC CAAGACAATT TNCANCTTCA AAAAGTTTTA TTAAANATTT 150  
 ACATTAGTTT TGTTGATGAG GATGACAAGA TTTTGGTCAT CAATTACATA 200  
 TACCCAAATT GAATAGTAAG CAACTTCAAT GTTTTTCATA ATGATAATGA 250  
 CAGACACAAN NNAAACCCAT TTATTATTCA CATTGATTGA GTTTTATATG 300

|                                                        |      |
|--------------------------------------------------------|------|
| CAATATAGTA ATAATAATAA TATTTCTTAT AAAGCAAGAG GTCAATTTTT | 350  |
| TTTAAATTAT ACCACGTCAC TAAATTATAT TTGATAATGT AAAACAATTC | 400  |
| AAATTTTACT TAAATATCAT GAAATAAACT ATTTTATAA CCAAATTACT  | 450  |
| AAATTTTCC AATAAAAAA AGTCATTAAG AAGACATAAA ATAAATTTGA   | 500  |
| GGTAAANGAG TGAAGTCGAC TGACTTTTTT TTTTTTATC ATAAGAAAAT  | 550  |
| AAATTATTAA CTTTAACCTA ATAAACACT AATATAATTT CATGGAATCT  | 600  |
| AATACTTACC TCTTAGAAAT AAGAAAAAGT GTTCTAATA GACCCTCAAT  | 650  |
| TTACATTAAA TATTTTCAAT CAAATTTAAA TAACAAATAT CAATATGAGG | 700  |
| TCAATAACAA TATCAAAATA ATATGAAAAA AGAGCAATAC ATAATATAAG | 750  |
| GGACGATTTA AGTGCGATTA TCAAGGTAGT ATTATATCCT AATTTGCTAA | 800  |
| TATTTGNGCT CTTATATTTA AGGTCATGTT CATGATAAAC TTGAAATGCG | 850  |
| CTATATTAGA GCATATATTA AAATAAAAAA ATACCTAAAA TAAAATTAAG | 900  |
| TTATTTTATAG TATATATTTT TTTACATGAC CTACATTTT CTGGGTTTTT | 950  |
| CTAAAGGAGC GTGTAAGTGT CGACCTCATT CTCCTAATTT TCCCCACCAC | 1000 |
| ATAAAAATTA AAAAGGAAAG GTAGCTTTTG CGTGTTGTTT TGGTACACTA | 1050 |
| CACCTCATTA TTACACGTGT CCTCATATAA TTGGTTAACC CTATGAGGCG | 1100 |
| GTTTCGTCTA GAGTCGGCCA TGCCATCTAT AAAATGAAGC TTTCTGCACC | 1150 |
| TCATTTTTTT CATCTTCTAT CTGATTCTA TTATAATTC TCTCAATTGC   | 1200 |
| CTTCAAATTT CTCTTTAAGG TTAGAATCTT CTCTATTTTT            | 1240 |
| GGTTTTTGTA TGTTTAGATT CTCGAATTAG CTAATCAGGC GCTGTTATAG | 1290 |
| CCCTTCCTTT TGAGTCTCTC CTCGGTTGTC TTGATGAAA AGGCCTAACA  | 1340 |
| TTTGAGTTTT TTTACGTCTG GTTTGATGGA AAAGGCCTAC AATTGGCCGT | 1390 |
| TTTCCCCGTT CGTTTTGATG AAAAAGCCCC TAGTTTGAGA TTTTTTTCT  | 1440 |
| GTCGTTGTT CTAAAGGTTT AAAATTAGAG TTTTACATT TGTGTTGATGA  | 1490 |
| AAAAGGCCTT AAATTTGAGT TTTCCGGTT GATTTGATGA AAAAGCCCTA  | 1540 |
| GAATTTGTGT TTTCCGTCG GTTTGATTCT GAAGGCCTAA AATTTGAGTT  | 1590 |
| TCTCCGGCTG TTTTGATGAA AAAGCCCTAA ATTTGAGTTT CTCCGGCTGT | 1640 |
| TTTGATGAAA AAGCCCTAAA TTTGAAGTTT TTTCCCCGTG TTTTAGATTG | 1690 |



```

TTTAGGTTTT AATTCTCGAA TCAGCTAATC AGGGAGTGTG AAAGCCCTAA 1740
ATTGAAGTTT TTTTCGTTGT TCTGATTGTT GTTTTTATGA ATTTGCAG 1788
ATG CAG ATC TTT GTG AAA ACT CTC ACC GGA AAG ACT ATC ACC 1830
Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr
 1 5 10
CTA GAG GTG GAA AGT TCT GAT ACA ATC GAC AAC GTT AAG GCT 1872
Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn Val Lys Ala
 15 20 25
AAG ATC CAG GAT AAG GAA GGA ATT CCC CCG GAT CAG CAA AGG 1914
Lys Ile Glu Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg
 30 35 40
CTT ATC TTC GCC GGA AAG CAG TTG GAG GAC GGA CGT ACT CTA 1956
Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu
 45 50 55
GCT GAT TAC AAC ATC CAG AAG GAG TCT ACC CTC CAT TTG GTG 1998
Ala Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val
 60 65 70
CTC CGT CTA CGT GGA GGT GGA TCC GCT GTT AAA AGA GTG GGT 2040
Leu Arg Leu Arg Gly Gly Gly Ser Ala Val Lys Arg Val Gly
 75 80
CGT AGG TTG AAA AAG TTG GAC CGT AAG ATT GAT AGG TTA GGA 2082
Arg Arg Leu Lys Lys Leu Asp Arg Lys Ile Asp Arg Leu Gly
 85 90 95
GTT GAT TTT TGATCTAGAG TCGACCGATC CCCC GAATTT CCCC GA 2127
Val Asp Phe
 100

```

## (97) INFORMATION FOR SEQ ID NO: 96:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2022
  - (B) TYPE: NUCLEIC ACID
  - (C) STRANDEDNESS: DOUBLE STRANDED
  - (D) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
  - (A) DESCRIPTION: GENOMIC DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96

```

TTTATCAATC AGATTTGAAC ATATAAATAA ATATAAATTG TCTCAATAAT 50
TCTACATTAA ACTAATATTT GAAATCTCAA TTTTATGATT TTTTAAATTC 100
ACTTTATATC CAAGACAATT TNCANCTTCA AAAAGTTTTTA TTAAANATTT 150
ACATTAGTTT TGTTGATGAG GATGACAAGA TTTTGGTCAT CAATTACATA 200

```

|                                                        |      |
|--------------------------------------------------------|------|
| TACCCAAATT GAATAGTAAG CAACTTCAAT GTTTTTCATA ATGATAATGA | 250  |
| CAGACACAAN NNAAACCCAT TTATTATTCA CATTGATTGA GTTTTATATG | 300  |
| CAATATAGTA ATAATAATAA TATTTCTTAT AAAGCAAGAG GTCAATTTTT | 350  |
| TTTTAATTAT ACCACGTCAC TAAATTATAT TTGATAATGT AAAACAATTC | 400  |
| AAATTTTACT TAAATATCAT GAAATAAACT ATTTTATATA CCAAATTACT | 450  |
| AAATTTTTC AATAAAAAA AGTCATTAAG AAGACATAAA ATAAATTGGA   | 500  |
| GGTAAANGAG TGAAGTCGAC TGACTTTTTT TTTTTTTATC ATAAGAAAAT | 550  |
| AAATTATTAA CTTTAACCTA ATAAAACACT AATATAATTT CATGGAATCT | 600  |
| AATACTTACC TCTTAGAAAT AAGAAAAAGT GTTCTAATA GACCCTCAAT  | 650  |
| TTACATTAAA TATTTTCAAT CAAATTTAAA TAACAAATAT CAATATGAGG | 700  |
| TCAATAACAA TATCAAAATA ATATGAAAAA AGAGCAATAC ATAATATAAG | 750  |
| GGACGATTTA AGTGCGATTA TCAAGGTAGT ATTATATCCT AATTTGCTAA | 800  |
| TATTTGNGCT CTTATATTTA AGGTCATGTT CATGATAAAC TTGAAATGCG | 850  |
| CTATATTAGA GCATATATTA AAATAAAAAA ATACCTAAAA TAAAATTAAG | 900  |
| TTATTTTTAG TATATATTTT TTTACATGAC CTACATTTTT CTGGGTTTTT | 950  |
| CTAAAGGAGC GTGTAAGTGT CGACCTCATT CTCCTAATTT TCCCCACCAC | 1000 |
| ATAAAAATTA AAAAGGAAAG GTAGCTTTTG CGTGTTGTTT TGGTACACTA | 1050 |
| CACCTCATTA TTACACGTGT CCTCATATAA TTGGTTAACC CTATGAGGCG | 1100 |
| GTTTCGTCTA GAGTCGGCCA TGCCATCTAT AAAATGAAGC TTTCTGCACC | 1150 |
| TCATTTTTTT CATCTTCTAT CTGATTTCTA TTATAATTTT TCTCAATTGC | 1200 |
| CTTCAAATTT CTCTTTAAGG TTAGAATCTT CTCTATTTTT            | 1240 |
| GGTTTTTGTA TGTTTAGATT CTCGAATTAG CTAATCAGGC GCTGTTATAG | 1290 |
| CCCTTCCTTT TGAGTCTCTC CTCGGTTGTC TTGATGGAAA AGGCCTAACA | 1340 |
| TTTGAGTTTT TTTACGTCTG GTTTGATGGA AAAGGCCTAC AATTGGCCGT | 1390 |
| TTTCCCCGTT CGTTTTGATG AAAAAGCCCC TAGTTTGAGA TTTTTTTTCT | 1440 |
| GTCGTTTCGTT CTAAAGGTTT AAAATTAGAG TTTTACATT TGTTTGATGA | 1490 |
| AAAAGGCCTT AAATTTGAGT TTTTCCGGTT GATTTGATGA AAAAGCCCTA | 1540 |
| GAATTTGTGT TTTTCCGTCT GTTTGATTCT GAAGGCCTAA AATTTGAGTT | 1590 |

|                                                         |            |            |            |             |      |
|---------------------------------------------------------|------------|------------|------------|-------------|------|
| TCTCCGGCTG                                              | TTTTGATGAA | AAAGCCCTAA | ATTTGAGTTT | CTCCGGCTGT  | 1640 |
| TTTTGATGAAA                                             | AAGCCCTAAA | TTTGAAGTTT | TTTCCCCGTG | TTTGTAGATTG | 1690 |
| TTTAGGTTTT                                              | AATTCTCGAA | TCAGCTAATC | AGGGAGTGTG | AAAGCCCTAA  | 1740 |
| ATTGAAGTTT                                              | TTTTCGTTGT | TCTGATTGTT | GTTTTTATGA | ATTTGCAG    | 1788 |
| ATG CAG ATC TTT GTG AAA ACT CTC ACC GGA AAG ACT ATC ACC | 1830       |            |            |             |      |
| Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr |            |            |            |             |      |
| 1 5 10                                                  |            |            |            |             |      |
| CTA GAG GTG GAA AGT TCT GAT ACA ATC GAC AAC GTT AAG GCT | 1872       |            |            |             |      |
| Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn Val Lys Ala |            |            |            |             |      |
| 15 20 25                                                |            |            |            |             |      |
| AAG ATC CAG GAT AAG GAA GGA ATT CCC CCG GAT CAG CAA AGG | 1914       |            |            |             |      |
| Lys Ile Glu Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg |            |            |            |             |      |
| 30 35 40                                                |            |            |            |             |      |
| CTT ATC TTC GCC GGA AAG CAG TTG GAG GAC GGA CGT ACT CTA | 1956       |            |            |             |      |
| Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu |            |            |            |             |      |
| 45 50 55                                                |            |            |            |             |      |
| GCT GAT TAC AAC ATC CAG AAG GAG TCT ACC CTC CAT TTG GTG | 1998       |            |            |             |      |
| Ala Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val |            |            |            |             |      |
| 60 65 70                                                |            |            |            |             |      |
| CTC CGT CTA CGT GGA GGT GGA TCC                         | 2022       |            |            |             |      |
| Leu Arg Leu Arg Gly Gly Gly Ser                         |            |            |            |             |      |
| 75                                                      |            |            |            |             |      |

## (98) INFORMATION FOR SEQ ID NO: 97:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 37
  - (B) TYPE: AMINO ACID
  - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
  - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97

Lys Arg Lys Arg Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu  
1 5 10 15  
Ala Arg Lys Ile Ala Arg Leu Gly Val Ala Lys Leu Ala Gly Leu Arg  
20 25 30  
Ala Val Leu Lys Phe  
35

## (99) INFORMATION FOR SEQ ID NO: 98:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 23
  - (B) TYPE: AMINO ACID
  - (C) TOPOLOGY: LINEAR
- (ii) MOLECULE TYPE:
  - (A) DESCRIPTION: PEPTIDE
- (iii) HYPOTHETICAL: NO
- (v) FRAGMENT TYPE: COMPLETE PEPTIDE
- (vi) ORIGINAL SOURCE: SYNTHETIC
- (vii) IMMEDIATE SOURCE: SYNTHETIC
- (x) PUBLICATION INFORMATION: NOT PREVIOUSLY PUBLISHED
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98

Ala Val Lys Arg Val Gly Arg Arg Leu Lys Lys Leu Asp Arg Lys Ile  
1 5 10 15  
Asp Arg Leu Gly Val Asp Phe  
20

## Claims

What is claimed is:

1. A polypeptide comprising a ubiquitin-lytic peptide fusion protein wherein ubiquitin is linked at its 3' terminus to a lytic peptide.  
5
2. The polypeptide of claim 1 wherein the ubiquitin polypeptide is described by sequence SEQ ID NO.: 94.  
10
3. The polypeptide of claim 1 wherein the lytic peptide is selected from the group consisting of cecropins, defensins, sarcotoxins, melittin and magainins.  
15
4. The polypeptide of claim 1 wherein the lytic peptide is a synthetic analog of a naturally occurring lytic peptide.  
20
5. The polypeptide of claim 1 wherein the lytic peptide is selected from SEQ ID Nos.: 1-91 and 97-98.  
25
6. A recombinant DNA molecule comprising a nucleotide sequence encoding a ubiquitin-lytic peptide fusion protein.  
25
7. The recombinant DNA molecule of claim 6 wherein the sequence encoding the 5' fusion ubiquitin peptide comprises nucleotide residues 921 to 1154 of SEQ ID NO.: 93.  
30
8. The recombinant DNA molecule of claim 4 wherein the sequence encoding the 3' fusion lytic peptide is selected from nucleotides sequences coding for the peptides of SEQ ID Nos: 1-91 and 97-98.  
35

9. The recombinant DNA molecule of claim 4 wherein the ubiquitin coding sequence is linked at its 5' end to a ubiquitin promoter.

5           10. An expression vector comprising a DNA sequence encoding a ubiquitin-lytic peptide fusion protein and a promoter sequence capable of directing the expression of such DNA sequence in a host cell transformed with such expression vector.

10           11. The expression vector of claim 10 wherein the DNA sequence of the vector includes the sequence of SEQ ID NO: 93.

15           12. The expression vector of claim 10 wherein the DNA sequence of the ubiquitin promoter and ubiquitin peptide sequence comprises nucleotide SEQ ID NO: 96.

20           13. The expression vector of claim 10 wherein the promoter is capable of directing expression in a prokaryotic host cell.

25           14. The expression vector of claim 10 wherein the prokaryotic host cell is an *Escherichia coli* cell.

            15. The expression vector of claim 10 wherein the prokaryotic host cell is an *Agrobacterium tumefaciens* cell.

30           16. The expression vector of claim 10 wherein the promoter is capable of directing expression in a eukaryotic host cell.

17. A ubiquitin-lytic peptide fusion protein producing host cell transformed with the expression vector of claim 10.

5           18. The ubiquitin-lytic peptide fusion protein producing host cell of claim 10, wherein said host cell is a plant cell.

10           19. The ubiquitin-lytic peptide fusion protein of claim 10, wherein said plant cell is a potato plant cell.

15           20. A method of expressing lytic peptides in cells comprising expressing a ubiquitin-lytic peptide fusion protein in a host cell.

20           21. The method of claim 20 wherein the expression of the ubiquitin-lytic peptide fusion protein is directed by a ubiquitin promoter.

22. The method of claim 20 wherein the ubiquitin-lytic fusion peptide protein is expressed in a eukaryotic cell.

25           23. The method of claim 22 wherein the ubiquitin-lytic peptide fusion protein is expressed in a plant cell.

30           24. The method of claim 23 wherein the ubiquitin-lytic peptide fusion protein is expressed in a potato plant cell.

35           25. The method of claim 20 wherein the ubiquitin-lytic peptide fusion protein is expressed in a prokaryotic cell.

26. The method of claim 25 wherein the ubiquitin-  
lytic peptide fusion protein is expressed in an  
*Escherichia coli* cell.

5           27. The method of claim 25 wherein the ubiquitin-  
lytic peptide fusion protein is expressed in an  
*Agrobacterium tumefaciens* cell.



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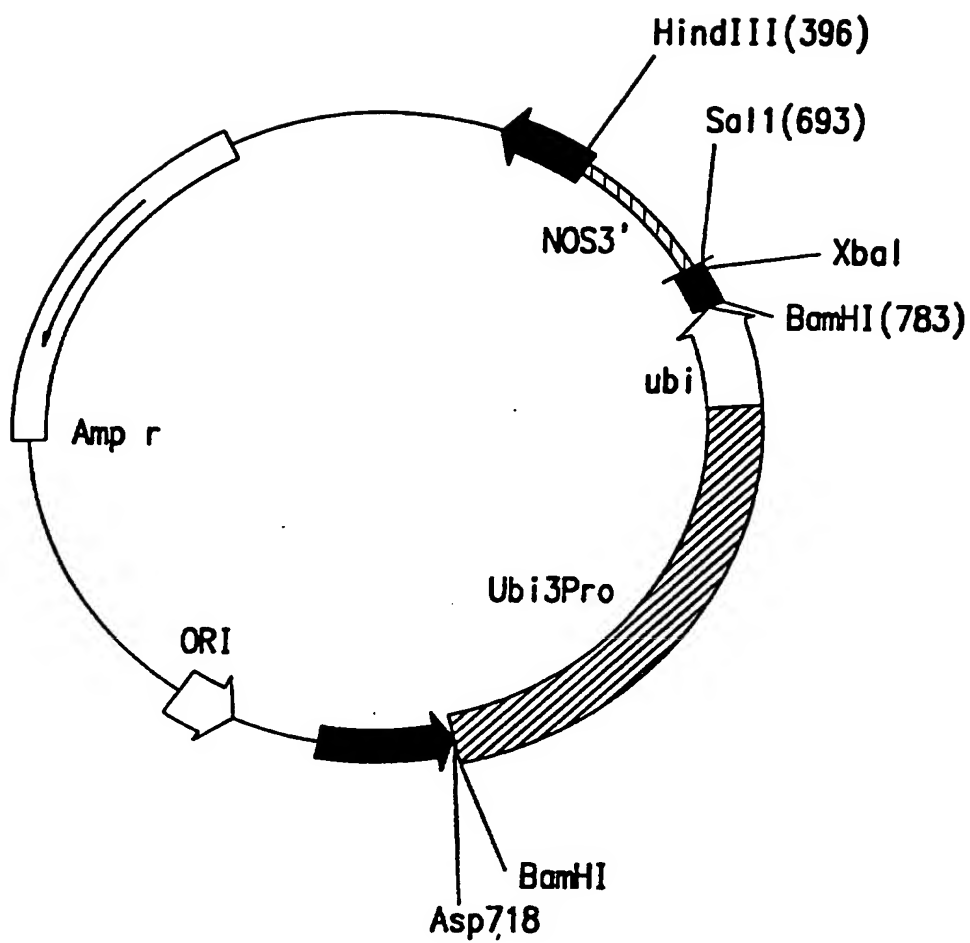


FIG.1

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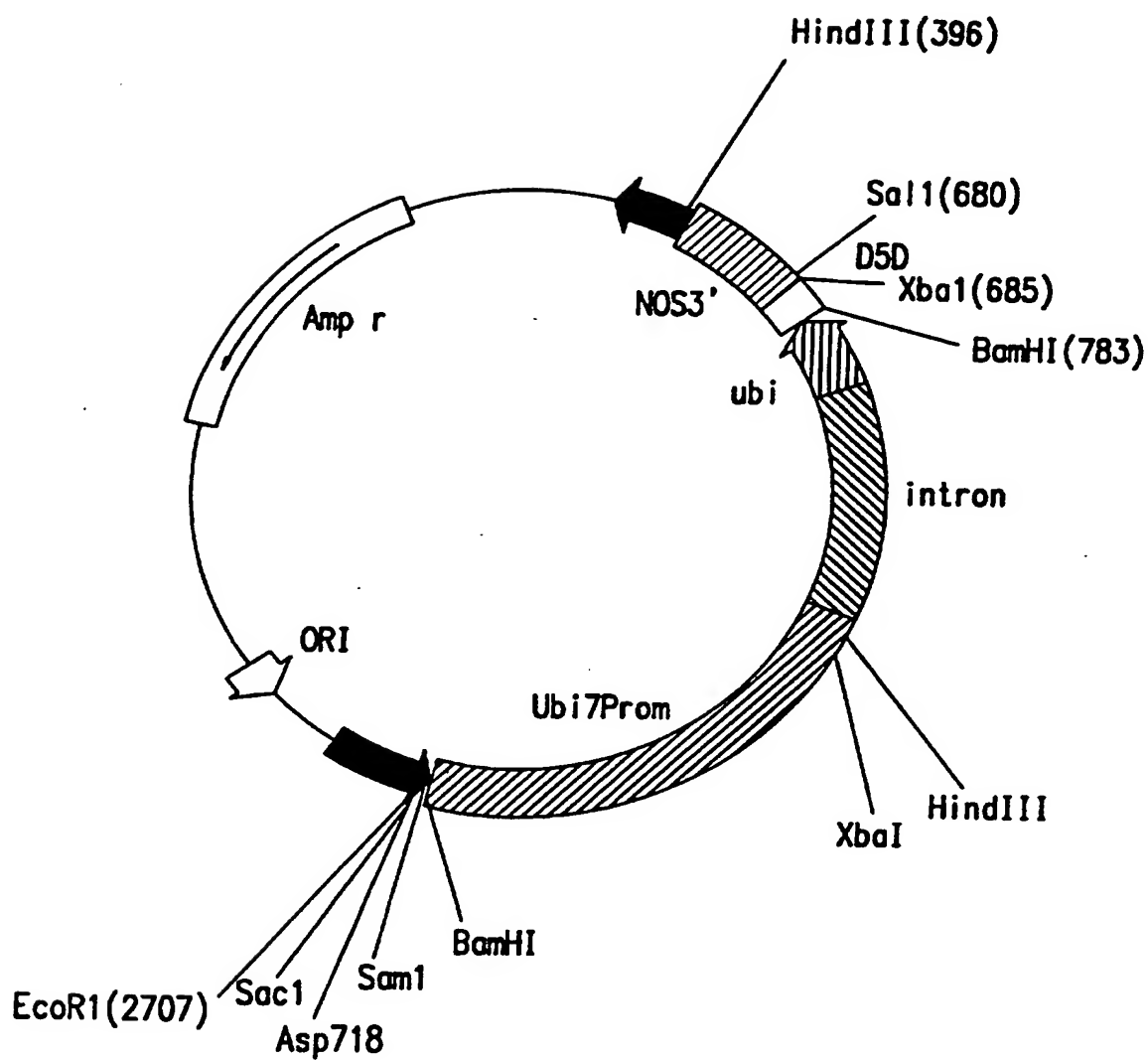


FIG.2

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US95/09339

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                 | Relevant to claim No. |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Y         | EP, A, 0342926 (LUBRIZOL GENETICS INC.) 23 November 1989, see entire document.                                                                                                                                                     | 1-27                  |
| Y         | WO, A, 90/12866 (LOUISIANA STATE UNIVERSITY AND AGRICULTURAL AND MECHANICAL COLLEGE) 01 November 1990, see entire document.                                                                                                        | 1-27                  |
| Y         | WO, A, 94/16076 (ZENECA LIMITED) 21 July 1994, see entire document.                                                                                                                                                                | 1-27                  |
| Y         | PLANT MOL. BIOL., Volume 24, issued 08 March 1994, GARBARINO ET AL., "Isolation of a ubiquitin-ribosomal protein gene (ubi3) from potato and expression of its promoter in transgenic plants", pages 119-127, see entire document. | 1-27                  |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

|                                                                                                                                                                         |     |                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents:                                                                                                                                | *T  | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |
| *A* document defining the general state of the art which is not considered to be of particular relevance                                                                | *X* | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                                                                     |
| *E* earlier document published on or after the international filing date                                                                                                | *Y* | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* | document member of the same patent family                                                                                                                                                                                                    |
| *O* document referring to an oral disclosure, use, exhibition or other means                                                                                            |     |                                                                                                                                                                                                                                              |
| *P* document published prior to the international filing date but later than the priority date claimed                                                                  |     |                                                                                                                                                                                                                                              |

Date of the actual completion of the international search

19 OCTOBER 1995

Date of mailing of the international search report

06 NOV 1995

Name and mailing address of the ISA/US  
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INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US95/09339

**A. CLASSIFICATION OF SUBJECT MATTER:**

IPC (6):

C12P 21/04; C07H 21/04; C12N 15/00, 5/00, 1/20

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL :

435/69.7, 252.2, 252.3, 252.33, 240.1, 320.1; 536/23.4

**B. FIELDS SEARCHED**

Minimum documentation searched

Classification System: U.S.

435/69.7, 252.2, 252.3, 252.33, 240.1, 320.1; 536/23.4

**B. FIELDS SEARCHED**

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN (Biosis, Biotechds, Ca, Cancerlit, Confsci, Dissabs, Embase, Jicst-E, Lifesci, Medline, Scisearch), lytic peptide#, cecropin#, defensin#, sarcotoxin#, melittin#, magainin#, fusion protein#, ubiquitin#, agrobacteri##, potato#